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THE EFFERENT PATHWAY FOR PUPILLARY CONTRACTION.

BY P. W. NATHAN AND J. W. ALDREN TURNER.

(From a Military Hospital for Head Injuries.)

IN this paper we are presenting evidence that there must be two separate pathways for efferent pupillo-constrictor fibres.

It is usually agreed that these pupillo-constrictor fibres leave the 3rd nerve nucleus and run with the nerve to the inferior oblique muscle; they branch off from this nerve to relay in the ciliary ganglion; distal to the ganglion, they form several short ciliary nerves which pierce the sclera around the optic nerve and form the ciliary plexus, from which fibres to the sphincter muscle of the iris are derived. It is thought that no fibres of the 3rd nerve reach the sphincter muscle of the iris by any other route.

If this is the only pathway by which constrictor fibres reach the sphincter, it follows that a complete interruption of this pathway will result in a pupil that reacts neither to light nor to convergence. There is evidence, however, that the interruption of this pathway can produce a pupil which does not react to light or darkness, but which contracts briskly on accommodation and convergence. It follows that some other pathway must be available.

Anderson (1905), Hodes (1940) and others have shown that in the cat extirpation of the ciliary ganglion produces a pupil which does not react to light or darkness. But in various species of apes, including chimpanzees, Foerster, Gagel and Mahoney (1936) recorded that after removal of the ciliary ganglion, the pupil still contracted on convergence. This experiment showed that there must be two efferent pathways for pupillary contraction, one subserving the light reflex which passes through the ciliary ganglion; the other concerned in the contraction of the pupil which accompanies the voluntary act of convergence, running to the sphincter muscle by some other route.

If indeed there are two efferent pathways for pupillary contraction, it might be expected that clinical cases would occur in which there is a paralysis of one function without the other. We have collected ten such cases, two of our own and eight from the Continental literature; we have not found any cases described in English.

In order to be sure that the lesion is in the efferent pathway and that the afferent path is intact, the following criteria are necessary: (*a*) the pupil on the normal side must contract when the affected eye is illuminated; (*b*) the affected pupil must not constrict to light or dilate in darkness either directly or consensually; (*c*) both pupils must contract normally on accommodation and convergence and dilate again afterwards; (*d*) the lesion must be known to be peripheral.

Case 1.—Lance-Corporal Sm., aged 22.

On May 25, 1940, he was hit by a piece of trench mortar shell just below and lateral to the right eye in the malar region. He remembers feeling the blow and having a sensation of being spun round and then falling down. Immediately after the injury his right eye closed. He had a severe right-sided headache. Three days after the injury he noticed that when he raised the right lid with his finger he saw double on looking upwards or downwards, but not laterally. The right side of his face felt numb.

On June 1 it was stated that the right pupil was dilated and immobile, that ptosis was present on the right and that there was complete loss of upward movement and impairment of downward movement of the right eye.

On June 3 he could raise the lid a little, but movements of the eye inwards, downwards and upwards were still grossly impaired; the pupil was still dilated and immobile.

March 3, 1942. Wing Commander Keith Lyle reported: "Right pupil—Almost absent reaction to light, both direct and consensual. Left pupil—Reacts briskly both directly and consensually. Both pupils react well on convergence. The right eye shows an upper field defect, especially on the nasal side; it shows no absolute scotoma, but a central relative scotoma for blue; the patient perceives red and green objects more clearly some distance from the fixation point, i.e. there is a right optic nerve lesion. There is slight pallor of the right optic disc. There is diplopia on extreme dextro-depression." He had complete anosmia on the right side (left side normal). He had absent corneal sensation on the right, anæsthesia and analgesia over the distribution of the right 5th nerve, gross wasting of the right temporalis muscle and some wasting of the right masseter; the jaw deviated to the right on movement. There was loss of taste on the right half of the tongue; facial movements were normal. To test the sympathetic supply of the face a sweating test was performed by Dr. L. Guttmann; it was normal.

The lesion in this case was certainly peripheral. The foreign body entered the cranium through the zygomatic process of the maxilla and came to rest on the floor of the middle fossa above the foramen ovale, beneath the right temporal lobe, as demonstrated by X-rays. At the time of the injury there was no loss of consciousness.

Over two years after the injury the pupil remains almost completely inactive to light and darkness, but contracts briskly on accommodation and convergence; the unaffected pupil reacts normally to direct and consensual illumination.

Case 2.—Gunner Sergeant, aged 29.

On November 11, 1941, the wheel of a gun passed over his head. He did not lose consciousness, and he had no amnesia for the event. For the first day he had a severe headache, but has had none since. He was taken to the Cambridge Hospital, Aldershot, and seen by Major C. J. B. Murray, who reported that the right eye showed marked ptosis and that it could not be opened voluntarily; the pupil was moderately dilated and fixed; there was also an external ophthalmoplegia. The patient could not see anything with that eye except a very bright light. The left eye was normal. By November 15 the patient could see objects clearly on the right, but the internal and external ophthalmoplegia remained. He was transferred to this hospital and was seen by Captain Llewellyn-Smith on December 2, who noticed that the right disc was a little paler than the left. Radiograms showed fractures of the roof of the right orbit, through the right optic foramen (without apparent compression), and of the greater wing of the left sphenoid. On December 4 Wing Commander Keith Lyle reported that on illuminating the left eye no response was shown by the right eye, but that the left pupil contracted when the right eye was illuminated. On January 1 visual acuity on the right was $\frac{6}{6}$, on the left $\frac{6}{5}$; there was still some degree of ptosis and the right pupil was slightly larger than the left. The external ocular movements were normal.

By April 28 the right pupil had become small; it reacted briskly on accommodating. No contraction was seen in the right pupil when the left was illuminated, the consensual reflex from right to left remaining normal. On illuminating the right eye directly very slight contraction of the pupil could be seen through a loupe.

By June 18 the right pupil could be seen to contract definitely in bright sunlight, and on July 17 some contraction could be seen on illuminating it with a small electric torch.

In this case the site of the lesion was the right sphenoidal fissure. The case fulfills our three criteria showing that the lesion is in the efferent pathway.

Case 3.—Described by Bollack (1919).

A man, aged 21, was wounded by a shell exploding three metres away. He did not loss consciousness but noticed something the matter with his right eye. He was examined that evening and found to have a penetrating wound of the lower eyelid, with slight enophthalmos and displacement of the globe upwards. There was a crossed diplopia, with maximum separation on looking down and to the right. There was a complete paralytic mydriasis and paralysis to accommodation. Radiography showed a foreign body deep in the orbit, 3 mm. long, situated about 5 cm. in, near the medial wall. Two months later he complained of diplopia, chiefly on looking down. Examination with red and green glasses showed a paralysis of the right inferior rectus and inferior oblique. The pupils were unequal, the right one being slightly meiotic. The right iris was normal. The pupillary reflexes were absolutely normal on the left, on the right direct light gave no contraction of the sphincter; on illuminating the left eye there was no contraction of the right pupil. The contraction of the pupil to accommodation-convergence was on the contrary absolutely normal. Instillation of atropine into the right conjunctival sac gave a maximal dilatation. There was also hypoæsthesia of the right cornea, given an inconstant corneal reflex. Visual acuity on both sides was $\frac{9}{10}$. Two months later the signs were the same.

The patient did not lose consciousness and had no amnesia for the event. The peripheral site of the lesion is clearly established. An important point in this case was the presence of a paralysis of the inferior oblique. It is the nerve to the inferior oblique that gives off the motor root to the ciliary ganglion; if this root is presumed to be paralysed, the case is a clinical counterpart of Foerster, Gagel and Mahoney's gangliectomized apes. Bollack considers that the absence of corneal reflex without involvement of the 5th nerve is further evidence that the ciliary ganglion is the site of the lesion. The author suggests that the ciliary ganglion may be the site of the lesion which causes the Argyll Robertson pupil.

Case 4.—Described by Magitot (1920).

A woman, aged 47, had a tumour weighing 7 gr., the size of a pigeon's egg, removed from behind the left globe; it was a typical angeioma. It left her with a paralysis of the left external rectus and a pupil which reacted neither to direct or consensual light, but reacted to accommodation. Visual acuity .

The author points out that the case is interesting as it shows an Argyll Robertson pupil which is incontestably due to a local cause. The photomotor reflex was seen to be quite normal before operation. At the same time as the sign appeared hypo-æsthesia of the supero-internal quadrant of the cornea was found. The tumour was too far anterior to involve the ciliary ganglion.

Case 5.—Described by Velter (1913).

A man, aged 58, attempted suicide by putting two revolver bullets into his right temple. He then found he had disturbance of vision and diplopia, which persisted for more than eighteen months; the right pupil was at first fully dilated, but gradually it has come down. On examination, the left eye was normal, the visual acuity was $\frac{6}{6}$. The right eye showed slight enophthalmos; there was no ptosis. The pupil was meiotic and contrasted with the left pupil, which was moderately dilated; the pupillary contour of the iris was slightly irregular. Contraction to accommodation-convergence was normal; but the light reflex direct and consensual (illuminating the left eye) was abolished; the consensual light reflex (illuminating the right eye) was present on the left. The optic disc was pale, with sharp margins and narrow vessels, the retina normal. The orbital muscles functioned normally, except for the internal rectus, which was incompletely paralysed; there was diplopia on looking to the right. Eighteen months later there was no change. Radiography showed both bullets in the right orbit, against the medial wall. Velter terminates his paper by pointing out that the case shows that the Argyll Robertson pupil can have an orbital cause.

Case 6.—Described by Abelsdorff (1906).

This patient showed a left-sided pupillary paresis following a recovered left-sided oculo-motor paralysis. He was also left with a paresis of the inferior oblique. The left pupil, which even under a bright light was wider than the right, reacted neither directly nor consensually to light, but reacted promptly to convergence, while the right pupil was normal in every respect.

This case also shows a peripheral Argyll Robertson pupil associated with a paralysis of the inferior oblique.

Case 7.—Described by Genet (1926).

A patient, aged 22, was wounded on June 26, 1925, in a car smash; sitting in the back of the car, he hit his face against the back of front seat; he was also cut by glass splinters. On examination, there was an ecchymosis of both lower lids, accompanied by a subconjunctival hæmorrhage on the left. The left pupil

was slightly dilated and showed "diminution of the reflexes of light and convergence." Vision was normal, after correction of a slight hypermetropia. On July 28 the patient returned on account of diplopia. It was due to a paralysis of the superior oblique. By February 19, 1926, the diplopia had disappeared. The pupil of the left side (the side of the trauma) was a little smaller than that of the right; it was regular, but did not react to light; it remained immobile both on direct and consensual illumination. The reflex to convergence was very brisk. The right pupil was absolutely normal; it reacted very well to direct or consensual illumination and to convergence.

The author adds that this case really has the value of a physiological experiment, because the patient was seen directly after the trauma; he did not consider that the abnormality was in the ciliary ganglion, "but in the intraocular nervous system itself."

Case 8.—Case described by Axenfeld (1906).

A 55-year-old woman fell on the right side of her face without signs of commotio cerebri. Examination showed diplopia, which disappeared in a few months. There was a paresis of the superior rectus. The right pupil was smaller than the left, and did not react to light directly or consensually. With a loupe, however, some movement was just visible. It reacted to convergence.

Case 9.—Described by Cosmettatos (1905).

A man, aged 60, received a blow in the right eye. The right pupil was in incomplete mydriasis and circular; the light reflex was completely abolished; constriction on accommodation, however, was normal. The consensual reflex was also absent in this eye when a light was shone into the non-affected eye. Myotics had no effect. The patient volunteered the information that the mydriasis was present immediately after the injury, and had not changed.

Case 10.—Described by Caspar (1906).

A man, aged 47, had fallen on his left eyebrow seventeen years previously. At first he saw double on looking down. The right pupil, 3 mm. diameter, reacted normally. The left pupil, 2 mm. diameter, did not react to direct or consensual light; but it contracted on accommodation and more on convergence. Visual acuity was $\frac{5}{5}$ in both. Five years later there was no change.

Discussion.

These cases provide evidence that the Argyll Robertson pupil can be caused by injury to the efferent pathway to the pupil. The occurrence of the Argyll Robertson pupil phenomenon may be accounted for in one of two ways: it can be assumed either that the damaged, known pathway allows the passage of only the strongest impulses and not of the weaker ones, and that the accommodation-convergence synkinesia is a much stronger stimulus than the light reflex; or that there must be two pathways. The first possibility does not accord with Foerster, Gagel and Mahoney's experimental work. If the 3rd nerve recovering from injury showed this selective sensitivity to the accommodation-convergence synkinesia, all cases of recovering 3rd nerve paralyses should go through a state of having Argyll Robertson pupils; this does not occur. Finally, one might expect in

some cases to find an intermediate stage of absent light reflex with defective contraction on convergence; but, like the eight authors cited above, we stress that contraction on convergence is quite normal and brisk in these cases. Thus, it seems justifiable to conclude that two efferent pathways exist.

Following head injury Argyll Robertson pupils of central origin also occur; we have seen several cases; others have been described by Aliquò-Mazzei (1934), Axenfeld (1906), Finkelnburg (1914), Genet (1934) and Harris (1938). The above cases, however, show that the Argyll Robertson pupil may be caused by a lesion in the peripheral efferent path—which was categorically denied by Kinnier Wilson (1921).

Similar pupillary abnormalities may occur in herpes zoster, where, presumably, the lesion is peripheral. Cases have been reported by Guillain, Lagrange and Périsson (1926) and by Valière-Vialeix (1931). Unfortunately there is no report of the histology of the ciliary ganglion in such cases; but in cases of ophthalmic zoster with normal pupillary reactions, the histology of the ciliary ganglion has been found to be normal (Lauber, 1903).

It is known that the efferent pathway of the light reflex runs through the ciliary ganglion. The pathway for the efferent fibres which conduct the impulse to contract on accommodation and convergence is unknown. We have considered the following possible routes:—

(1) via the sympathetic.
(2) via the external ocular muscles.
(3) via the optic nerve.
(4) via the naso-ciliary nerve.
(5) via the long ciliary nerve.

(1) *Via the sympathetic.*—These fibres cannot run to the ciliary body via the sympathetic for the following reasons. In extirpation of the sympathetic system in animals and in Horner's syndrome in man, there is no disturbance of pupillary constriction on convergence, and in cases where there is stimulation of the cervical sympathetic, there is also no change, as in the case described by Mounier-Kuhn (1931).

The possibility must be considered that the sympathetic may be concerned in these pupillary movements in addition to the 3rd nerve. It may be that whenever the 3rd nerve is stimulated, the pupillary sympathetic is reciprocally inhibited; this reciprocal inhibition will still take place when the 3rd nerve is cut, and will manifest itself in pupillary movements. But, in fact, this does not take place; no pupillary

movements are seen in eyes where the 3rd nerve has been damaged completely. The pupils in our cases responded to homatropine physostigmine and pilocarpine—drugs which act on the para-sympathetic system. After atropinization there was no pupillary movement; but if impulses were travelling via the sympathetic, atropine would not affect them; and one would see contraction and dilatation of the pupil in the fully atropinized eye.

(2) *Via the ocular muscles.*—It seemed possible to us that these fibres might reach the pupil by running along the external ocular muscles, through their tendons and into the sclera to join the ciliary plexus. Although no typical myelinated fibres like the short ciliary nerves have been described, Sherrington and Tozer (1909) have described a few sparse myelinated fibres, size 2 to 5 μ, running into the tendons of these muscles. In order to investigate this possibility, we have cut and stimulated the muscles to the eye in four human subjects undergoing strabotomies. We used sodium pentothal anæsthesia without premedication, so as to avoid the effects of morphia, atropine or cocaine on the pupil. The muscles were stimulated by a unipolar electrode using a current which was sufficient to cause contraction. The muscles examined were the internal rectus, the inferior rectus and the superior rectus. In no case was any pupillary change observed.

Furthermore, Cushing (1905) and Harris (1938) have reported cases in which, following injection of the 5th nerve in the foramen rotundum, there was a paralysis of the external ocular muscles supplied by the 3rd nerve, while the pupils continued to react well both to light and accommodation. In these cases the pathway for pupillary contraction cannot have been via the muscles supplied by the 3rd nerve.

Sherrington (1893) stimulated the root of the 6th cranial nerve in the monkey, but could not satisfy himself that there was any resulting contraction of the pupils.

(3) *Via the optic nerve.*—These fibres cannot run via the optic nerve as contraction on convergence still remains when this nerve has been completely destroyed.

(4) *Via any branch of the 5th nerve.*—These impulses cannot travel via the nasociliary nerve, or the long ciliary nerves to the globe, for pupillary contraction on accommodation remains normal with complete lesions of the 5th nerve and pupillary contraction is absent in complete lesions of the 3rd nerve, when the 5th nerve is intact. Cases which show involvement

of the nasociliary nerve are not associated with disturbance of pupillary contraction.

It will be seen, then, that although there appear to be two efferent pathways for fibres causing pupillary contraction, we have no positive evidence of any route, except that passing through the ciliary ganglion, which could be used to account for the peripheral Argyll Robertson pupil.

There is, however, one other possible pathway. Axenfeld showed in 1907 that just proximal to the sclera or in the scleral canals, ganglion cells were frequently found on the ciliary nerves; he found up to thirty of them, and named them episcleral ciliary ganglia. They not only supply the choroid, but also supply a mass of fibres to the ciliary muscle; like the other short ciliary nerves, they are myelinated, their terminal divisions losing their myelin sheaths when they come to lie as small bundles of fibrillæ in the stroma of the ciliary body—as originally described by Agababow (1892). More recent work by Givner (1939) shows that these episcleral ganglia are not only common, but are probably a normal structure; he found them in ten consecutive eyes which he examined; his paper contains excellent photomicrographs of these nerves and ganglia.

Here is a possible alternative pathway, which avoids the ciliary ganglion. It is possible that the fibres which take this path are those concerned with the accommodation-convergence synkinetic contraction and not with the light reflex; but no positive evidence on this point has yet been obtained.

It may be added that this mode of innervation is typical of the parasympathetic pattern, as seen, for example, in the submaxillary gland. Langley (1885) has shown that the parasympathetic fibres supplying the gland arise from the ganglion cells lying within the hilum of the gland and not only from the submaxillary ganglion. In the same way it is possible that the parasympathetic pupillo-constrictor fibres relay not only in the ganglion cells of the ciliary ganglion, but also in the more peripherally situated episcleral ciliary ganglia.

Summary.

(1) Evidence is presented to show that there are two efferent pathways for pupillary contraction; one serving the light reflex, the other serving the accommodation-convergence synkinesia.

(2) Cases are described and cases already recorded are summarized, which show that the Argyll Robertson pupil may be caused by damage to the peripheral efferent pathway to the pupil.

(3) Various paths for the synkinetic pupillary contraction are considered, and experimental work on man in this connection is presented.

(4) It is possible that the fibres concerned in the synkinetic contraction of the pupils on accommodation and convergence run from the 3rd nucleus to the episcleral ciliary ganglia, thence relaying to the ciliary body, without passing through the ciliary ganglion.

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OLIGODENDROGLIOMATOSIS OF THE CEREBROSPINAL PATHWAY.

BY DIANA J. K. BECK[1] AND DOROTHY S. RUSSELL.[2]

(From the Nuffield Department of Surgery, Oxford.)

ALTHOUGH the oligodendrogliomas have in the past been regarded as benign it has recently been observed that they tend to recur after operation (Eisenhardt, 1937), and that they may display a sudden increase in the rate of growth after a long period of relative inactivity (Elvidge, Penfield and Cone, 1937). The frequent occurrence of mitotic figures in these tumours was noted in both of these reports. The possibility that they may spread to other parts of the central nervous system by metastasis was first pointed out by Cairns (1929) in his description of ependymal deposits in the occipital horns and 4th ventricle of a subject from whom a right frontal oligodendroglioma had been removed three and a half years previously. In 1931 Purdon Martin reported a case in which a diffuse ventricular spread of the tumour was found nine months after resection of a left parietal oligodendroglioma. In 1933 Greenfield and Robertson described a further case in which diffuse ventricular spread complicated a cystic oligodendroglioma of the right frontal lobe and, in addition, a similar glioma (Case 5) of the 4th ventricle which was accompanied by discrete secondary deposits in the interpeduncular space and suprapituitary region. The latter forms the first established instance in which this type of tumour had spread to the leptomeninges by way of the cerebrospinal fluid. Greenfield and Robertson considered metastatic spread of oligodendrogliomas along the cerebrospinal pathway to be very rare. No such example was identified either at the London Hospital or in this department before 1938. Since then 4 cases have been recognized, and they are described in the present communication.

Case 1.—R. I. 4571. In 1931, when he was 29 years old, G. W., a clergyman, began to have attacks in which for a moment he lost the thread of what he was saying, and at times saw lights on his right side and experienced an unpleasant taste. In 1934, after mumps, he began to have frequent and at times incapacitating frontal and generalized headaches with nausea and sometimes vomiting. These headaches were often accompanied, for a period of up to half an hour, by a nasty taste which seemed to go down towards his epigastrium, difficulty in finding words

[1] William Gibson Research Scholar, Royal Society of Medicine.

[2] Working for the Medical Research Council.

and in reading, and by tingling sensations in his tongue, the roof of his mouth, and both hands. The headaches lasted up to eighteen hours and left him with a stiff neck. In January, 1935, he had his first convulsive attack, preceded by the visual and gustatory aura and by a feeling of compulsion to turn his head and eyes to the right. He became increasingly tired and found that he could not preach without notes. In October, 1935, he gave up preaching.

Examination in November, 1935 (Dr. Riddoch and Mr. Cairns) showed a spare young man of normal intelligence and behaviour, without any impairment of speech. There was slight relative anosmia at the left nostril. His optic discs and visual fields were normal. Apart from fine tremor of the limbs, which he said he had always had, weakness of the right side of the face on smiling was the only other neurological sign. On *lumbar puncture* the resting pressure was over 300 mm. The protein content of the cerebrospinal fluid was 200 mg. per cent. and the white cells 1 to 2 per c.mm.

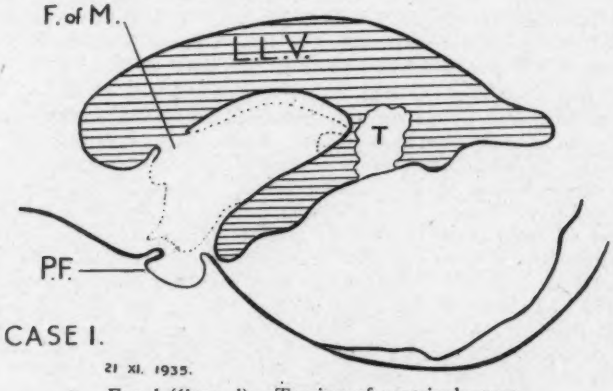

FIG. 1 (*Case 1*).—Tracing of ventriculogram.

Ventriculography (November 21, 1935) showed dilatation of the lateral and 3rd ventricles without displacement. There was an indentation of the lower border of the body of the left ventricle, which was interpreted as an inaccessible tumour (fig. 1). A right subtemporal decompression was performed. The patient recovered uneventfully from this operation and from this time onwards received periodic courses of deep X-ray treatment.

During the next twelve months he had only one attack of headache and vomiting; it was accompanied by shivering, cramps in both hands and tongue, a nasty taste, difficulty in speaking and tightness of the decompression. He returned to work in May, 1936. In November of the same year he had two attacks of unconsciousness and in April, 1937, another which was preceded by a peculiar feeling in the epigastrium and a sensation of unreality. During the latter part of 1937 he became tired again and had difficulty in preparing his sermons. When tired he would at times see shimmering lights on his right side.

Ventriculography (November 15, 1937) showed appearances similar to those seen two years before except that the defect in outline of the lower part of the body of the left lateral ventricle was rather more conspicuous. The fluid from each lateral ventricle contained 180 mg. per cent. of protein, with 2 to 6 cells per c.mm.

On this occasion ventriculography was followed by a severe reaction: the pulse-rate fell to 44 per minute, there were deep, sighing respirations, progressive drowsiness and complete global aphasia with moderate weakness of the right side of the face and right arm, and less pronounced weakness of the right leg. The right plantar reflex was extensor, the left equivocal. The menace reflex was absent on the right side. Apart from a persisting dyslexia, mental dullness and a definite attention defect in the left lower temporal quadrant of the visual field, all these signs cleared up in two days, though it was noticed that he had occasional vibratory tremors in the left limbs.

As a left posterior intraventricular tumour was suspected, a left posterior osteoplastic exploration was performed on November 29, 1937, but revealed nothing abnormal except whitish streaks and plaques about the leptomeningeal vessels. The post-operative reaction was severe: great restlessness, retention of urine, complete right homonymous hemianopia, and within twenty-four hours apraxia and a complete global aphasia were present. These symptoms were relieved, the hemianopia completely, by daily ventricular or lumbar puncture. The fluid was always blood-stained and at a pressure of about 400 mm. Four weeks after operation the patient was discharged, free from symptoms and with full visual fields.

Apart from a few minor attacks, in one of which he lost his way in his home and had to be guided by his sister, he remained fairly well until October, 1938, when he began to have severe hydrocephalic attacks and to show progressive mental deterioration. In the attacks there was great increase of the tension of the subtemporal decompression, slowed pulse, headache, stiffness of the neck, vomiting, retention of urine, depression of the tendon-jerks, restlessness and stupor, and generalized fits which were followed by temporary paralysis of the left arm and leg. Ventriculograms showed increase in the size of the ventricles. The symptoms were relieved for a time by withdrawal of fluid from the ventricles. The pressure of the fluid was about 600 mm.; it contained 210 mg. per cent. of protein and became increasingly blood-stained. The lumbar fluid, which was at the same pressure, contained 320 mg. per cent. of protein. He died in November, 1938, seven years after the onset of symptoms.

Summary of necropsy. (*R.I. P.M. No.* 286, 1938). *Internal hydrocephalus. Oligodendrogliomatosis of ventricles and leptomeninges.*—Hypostatic and inhalation bronchopneumonia. Gastric contents in both pleural sacs. Post-mortem digestion of fundus of stomach and of peri-œsophageal region of diaphragm. Absence of appendix (old operation); fibrous pericæcal peritoneal adhesions. No abnormality in remainder of abdominal and thoracic organs. Colloidal adenoma in right lobe of thyroid gland.

Examination of central nervous system. Macroscopic.—Brain: The dural venous sinuses appeared normal. The inner surface of the dura mater was coated with a thin layer of recent clot. Fibrous adhesions united the surface of the brain to adjacent tissues over the decompression areas in the right temporal and left occipital regions respectively. There was considerable herniation of the brain at the former site. Elsewhere the cerebral convexities were considerably flattened and their leptomeninges presented a greyish-white opacity suggestive of fibrosis. This thickening of the meninges was accentuated in the sulci, the Sylvian fissures and over the orbital surfaces of the frontal lobes. A similar dense fibrosis affected the meninges over the whole of the base of the brain, the cisterna magna, dorsal surface of the cerebellum and about the great vein of Galen. The cisterna magna was enlarged, and over each foramen of Luschka was a cyst-like pouch formed by the thickened arachnoid membrane.

On section a recent hæmorrhage, measuring 3 by 3·5 by about 10 cm., occupied the centrum semiovale over the dorsomedial border of the occipital horn and body of the right lateral ventricle. There was softening and hæmolytic staining of the adjacent white matter, and a small quantity of blood-clot was present in the ventricle. The ependyma throughout the ventricles was thickened, opaque and in places coarsely granular. Embedded in the ventromedial wall of the vestibule of the left ventricle was a spheroidal tumour, 1·5 cm. in diameter, half of which projected into the ventricular cavity and corresponded to the mass observed in the ventriculograms. The cut surfaces of this tumour were lobulated and composed of soft grey granular tissue which was well demarcated from the surrounding white matter of the hippocampal gyrus. In addition conspicuous nodules of soft grey tissue, measuring up to 0·8 cm. in diameter, projected from the walls of the temporal and occipital horns on both sides, the left frontal horn, supraoptic recess and pillars of the fornix. The nodules were confluent over the septum pellucidum, forming a layer about 0·2 cm. deep, and thinner plaques were visible as geographical areas in the roof of the left ventricle. Pinhead and slightly larger granulations were present in the walls of the 4th ventricle, which was moderately dilated. The lateral ventricles were considerably and symmetrically dilated, and the iter measured 0·25 by 0·45 cm. in transverse section between the anterior and posterior corpora quadrigemina.

Spinal cord: The dura was united in places to the arachnoid membrane by delicate fibrous adhesions. The pia-arachnoid was matted by tough greyish-white fibrous tissue over the greater part of the posterior surface of the cord, especially in the mid-line where the thickening constituted a broad irregular longitudinal ridge. An interrupted sheet of similar tissue extended over the nerve roots, especially in the cauda equina where fusiform nodular expansions were visible in many places and adjacent roots were often matted together. A larger nodule, measuring 0·9 by 0·5 by 0·3 cm., projected from the right posterior root of the 11th thoracic segment. On section the subarachnoid space was reduced to relatively small compartments over the lateral and ventral aspects of the cord. The substance of the cord itself appeared normal at all levels.

Microscopic.—When hardened in formol-ammonium-bromide portions of the brain, spinal cord and nerve roots were either embedded in paraffin or cut on the freezing microtome. Paraffin sections were stained with Ehrlich's hæmatoxylin and eosin, Weigert's iron hæmatoxylin and van Gieson's mixture, phosphotungstic-acid hæmatoxylin, and toluidin blue for mucin. Frozen sections were impregnated with silver by a variety of methods.

The *tumour* in the vestibule of the left ventricle is well defined, unevenly lobulated and of heterogeneous structure. Some lobules, mostly near the surface, are composed of small polygonal and spheroidal, non-fibrillated cells in many of which the cytoplasm is vacuolated, while in others it forms a narrow irregular rim about the nucleus. Other lobules, mainly deep to the surface, are formed either of bundles of long bipolar fibrillated cells or of large, spheroidal and polygonal cells with coarsely granular cytoplasm surrounded by a tangle of neuroglial fibrils. The nuclei of these cells are pyknotic, or have undergone karyolysis. Towards the centre of the tumour one of the lobules is composed of closely crowded polygonal cells of variable size, most of which are multinucleate. Some of them possess a single short blunt process directed towards a neighbouring vessel and groups of these cells thus form pseudo-rosettes. In the centre of the tumour there is also an area of necrosis.

Elsewhere the *ependymal nodules and plaques* in the lateral ventricles are everywhere composed of spherical and polygonal cells resembling those forming the superficial parts of the tumour just described. These cells are relatively small, measuring from 8 to 10 μ, but are mostly about twice this size owing to cytoplasmic vacuolation (fig. 3). In the smaller cells the cytoplasm is homogeneous and is occasionally prolonged into a few short processes, but contains neither fibrils nor blepharoplasts. Many of the cells show advanced pyknosis, but in others the nucleus is spherical and contains one or two small nucleoli, a lightly staining nucleoplasm and a delicate chromatin net beset with nodes of varying size. Supporting blood-vessels are scanty, but groups of capillaries are occasionally present near the surface of the nodules. The walls of these, and of some of the deeper vessels in the nodules, show slight mucinous degeneration. There is marked proliferation of the astrocytes in the subependymal glia, and these cells have often undergone degenerative changes with clasmatodendrosis and the production of swollen "amœboid" forms. They resemble the large spheroidal cells in the deeper parts of the tumour in the left vestibule. A conspicuous microglial reaction is present about the ependymal nodules with the production of many transitional amœboid forms.

The *leptomeninges* over the base of the brain are greatly thickened by a fibrosis which varies in amount and density from place to place. It extends into the cerebral sulci and forms a dense mat round the olfactory processes. Over the cerebellum the thickening is greatest over the summits of the folia, and the sulci are seldom involved. In the meshes of the collagenous fibres are numerous spindle fibroblasts, scanty lymphocytes and plasma cells, and large numbers of spheroidal and polygonal mononuclear cells (fig. 6). These are often indistinguishable from the cells composing the ependymal nodules. They are, however, undoubtedly mixed with desquamated arachnoid cells and may often be confused with the latter when they are in the stages preparatory to active phagocytosis. There is no change in the adjacent brain tissue apart from moderate degrees of marginal gliosis.

In the *spinal cord* there is gross thickening by fibrosis of the pia-arachnoid with the formation of a crescentic mass over the posterior aspect tapering towards the ventral surface. The ligamenta denticulata participate in this thickening, producing great constriction of the subarachnoid space (fig. 5). The cellular infiltration of the fibrous tissue is similar to that present over the brain, but is in general much sparser. The spheroidal cells often line the residual compartments of the subarachnoid space and form small groups in the meshes of the collagen and about the posterior roots. The spinal cord itself is unaltered.

The *nerve roots* are frequently invaded by the spheroidal cells, which form in places nodular expansions, especially in the cauda equina (fig. 7). Many of these nodules are densely fibrotic, but some have little connective-tissue stroma and in these the cells are often separated by a homogeneous coagulum which, in some areas, stains faintly for mucin. The nerve fibres involved in these foci of infiltration show progressive degeneration of their myelin sheaths in suitably stained preparations (fig 4), and of their axis-cylinders in Gross-Bielschowsky preparations.

Comment.

From its size, structure and early recognition by means of ventriculography it seems permissible to regard the spherical mass in the left

lateral ventricle as the primary tumour in this case. Histologically it is a mixed glioma, being composed both of oligodendroglial cells and of astrocytes of various types. Moreover, there is evidence, in a central area, of the anaplastic changes usually regarded as characteristic of spongioblastoma multiforme. It is not uncommon for oligodendrogliomas to contain considerable numbers of astrocytes or even areas that are indistinguishable from fibrillary astrocytoma. It is gradually coming to be recognized that any of the more differentiated gliomas may in time undergo anaplasia, acquiring the malignant features of spongioblastoma multiforme (Cox, 1933), and it is probable that many of this class of tumours arise in this way. We have previously observed anaplastic changes in several examples of cerebral oligodendroglioma.

It is clear from the histological examination that the pronounced meningeal fibrosis and the ependymal nodules were due to the dissemination by the cerebrospinal fluid of cells uniformly of oligodendroglial type. The pronounced fibrosis of the leptomeninges, giving an appearance of chronic arachnoiditis on naked-eye examination, and the long history are both features unique in our experience of diffusely metastasizing gliomas. They lead us to assume that dissemination antedated the anaplastic changes in the primary tumour and was not attributable to such changes. From the early ventriculographic evidence of internal hydrocephalus, obtained three years before death, it must be supposed that the dissemination had been in progress over an even longer period. The considerable spells of good health between attacks probably corresponded to periods during which dissemination was in abeyance. Irradiation therapy was not demonstrably responsible for this, and it is recognized that the oligodendrogliomas are not in general radiosentitive (Frazier and Alpers, 1937). The clinical diagnosis was difficult: certain features suggested a left temporo-occipital tumour, but in view of the long history and the absence of cells in the lumbar cerebrospinal fluid, a diagnosis of meningeal metastasis seemed unjustifiable. The abnormal outline of the left ventricle was certainly due to the mass discovered on examining the brain. The steady increase of protein in the fluid was against an interpretation of chronic arachnoiditis with secondary hydrocephalus. In retrospect it is possible to recognize certain clinical symptoms that may have been referable to the invasion of the meninges and spinal nerve roots by tumour cells: the stiffness of the neck that followed severe headaches in the earlier stages, and preceded two acute hydrocephalic attacks in the later stages of the illness, and the disturbance of bladder-function. It is, however,

possible that these signs were attributable to a temporary increase in the hydrocephalus for, apart from such episodes, there was a persistent and striking paucity of physical signs.

Case 2.—C. M., a storekeeper, aged 42, was admitted to the London Hospital on June 10, 1939, on account of attacks of unconsciousness, headache and failure of vision.

Apart from a minor motor-cycling injury fifteen years previously the patient had been in good health until eighteen months before admission. He then began to have "queer turns," diagnosed by his private doctor as *petit mal*. At first these occurred at long intervals, but they gradually increased in frequency until he had as many as three to four in a day. Long warnings of dizziness, lasting from two to three hours, occasionally preceded the attack, and for six months a taste of sulphur had been followed by immediate loss of consciousness. He collapsed instantly without ever injuring himself and was incontinent of urine. There were no convulsive movements apart from opening and closing of the hands. The attacks lasted from ten to thirty minutes, occasionally forty-five minutes, and were followed by a feeling of illness and feebleness lasting about three hours, during which he was sleepy, disorientated and, of late, blind. For ten months the attacks had been associated with occipital headache, and this occurred at other times, usually lasting an hour or two without any relief on change of posture.

For a year before admission his sight had gradually failed. He also had severe attacks of pain, at first in the right and later in the left side of the chest, and at the base of the spine. Radiographic examination of the chest and spine was negative. His speech was disturbed: he would say strange things and misnamed objects. He was aware of being unable to find a word, getting it, and then losing it again before he could make use of it. Dismissed from his job seven months before admission to hospital, and unable to find another because of his fits, he became depressed and lost his appetite to such a degree that he had to be fed. Although there was neither dysphagia nor vomiting he had wasted rapidly. He became increasingly childish, especially after attacks, but there was no fundamental change in his temperament. During the month before admission he had precipitate and difficult micturition followed by complete loss of bladder-control. For three weeks he had had recurrent attacks of severe pain in the back and in the right side of the upper abdomen of such severity as to raise the question of an acute abdominal catastrophe. He became restless to the point of violence by night and drowsy by day.

Examination.—He appeared very ill, being wasted and dehydrated. He was slow and apathetic although rational and co-operative. Memory and intellectual capacity were poor. There was no manifest motor aphasia. Perception of smell was much less acute on the right than on the left side. The right eye was completely blind and the visual acuity on the left $\frac{6}{8}$ with a full visual field. The right optic disc showed a doubtful early secondary atrophy on the nasal side, whereas on the left there was swelling of about 1 dioptre on the nasal side with a clear temporal edge. There was slight bilateral proptosis and ptosis. The pupillary reactions corresponded to the state of his eyesight and there was at times a divergent squint. The left corneal reflex was depressed, and the appreciation of pin-prick over the distribution of the left 5th cranial nerve was diminished. There was a left lower facial weakness.

His left upper limb was slightly weak and ataxic, and its tendon reflexes were increased. Both legs were atonic and weak, the latter quality being much more marked on the left side, where the tendon-jerks were brisker. The left abdominal reflexes were diminished and both plantar responses were extensor. Over the whole of the left side of the body there was diminished appreciation of pin-prick and he was unable to assess accurately the spatial relations of his left hand.

On the day after admission he had a brief but severe attack of right upper abdominal pain, with muscular resistance in the right upper quadrant which persisted for some days.

Radiographic examination of the skull showed gross destruction of the pituitary fossa, the dorsum sellæ and the lesser wings of the sphenoid. On lumbar puncture the cerebrospinal fluid was under a pressure of 460 mm., was orange and slightly blood-stained and contained 600 mg. per cent. of protein, 8,400 red cells and 11 white cells per c.mm.

The clinical appearance suggested the presence of carcinomatous cerebral metastases but the long history of neurological disturbance did not support this diagnosis. It was decided that he probably had a right frontal or fronto-temporal lesion. Ventriculography was not performed.

Operation, June 14, 1939: right osteoplastic flap. The dura was tense and without pulsation and, as the patient's condition was precarious, the right ventricle was tapped, the dura opened and a decompression effected without identification of tumour tissue. The cerebrospinal fluid from the right ventricle contained 120 mg. per cent. of protein and 3 white cells per c.mm.

Progress.—Following operation the patient was apathetic and disorientated. There was further impairment of memory, and perseveration without any obvious aphasia. His vision deteriorated to the point of appreciation of hand movements only with the left eye. The left side of his face and all his limbs became weaker. In spite of repeated punctures of the right ventricle, the osteoplastic flap bulged, and at the same time the paralysis of the left upper and lower limbs became complete. His limbs wasted, but all the tendon-jerks were grossly exaggerated. He fell into stupor and died on July 16, 1939.

Summary of necropsy. (L.H. P.M. 253, 1939).

Bronchopneumonia. Gliomatosis of leptomeninges. Oligodendroglioma of tuber cinereum. Operation: craniotomy.—Peribronchial pneumonic consolidation in lower lobes of both lungs. Slight purulent bronchitis in remainder of lungs. A few fragments of ante-mortem thrombus in branches of main pulmonary arteries. Obsolete tuberculosis in ventrolateral angle of right upper lobe, and in lymph nodes both of paratracheal region and tracheal bifurcation. Milk-spot in visceral pericardium over posterior surface of right ventricle. Slight fibrous thickening of centre of free margin of anterior cusp of mitral valve. Slight atheroma. Diffuse congestion of liver. No naked-eye abnormality in remainder of abdominal organs. Osteoporosis of ribs. Middle ears dry. Congenital abnormality: aberrant artery traversing left cavernous sinus and grooving left posterior clinoid process to unite internal carotid and basilar arteries. No visible alteration of pituitary body. A greatly wasted well-developed man.

Examination of central nervous system. Macroscopic.—Brain: Beneath the healed craniotomy wound in the right frontal region the frontal and temporal lobes were superficially torn and softened, especially about the Sylvian fissure. There was

diffuse tough pearly-grey thickening of the leptomeninges at the base of the brain, reaching its maximum (0·15 cm. thick) over the optic chiasm and left optic nerve, but fading away at the anterior end of the optic foramen. There was some atrophy of the right optic nerve without visible infiltration of its sheath. Elsewhere the infiltration extended over the orbital surfaces of the frontal lobes and along the Sylvian fissures, appearing more fibrous and less obviously neoplastic over the cerebral convexities, and throughout the posterior fossa.

On section a circumscribed spherical nodule (0·7 cm. in diameter) of pearly-grey tissue with a hæmorrhagic centre expanded the tuber cinereum, displacing the pituitary stalk anteriorly and uniting with the floor of the 3rd ventricle. Numerous miliary and submiliary pinkish-grey granulations studded the ependyma of both frontal horns, especially the left, and the proximal part of the 4th ventricle. The ependyma elsewhere was smooth and glistening. There was a moderate internal hydrocephalus. An old hæmorrhage, measuring 2 by 2·5 by about 4·5 cm. antero-posteriorly, occupied the white matter of the right frontal lobe beneath the site of operation, and a similar smaller hæmorrhage lay in the right superior temporal convolution. The remainder of the brain appeared normal.

Spinal cord.—The pia-arachnoid over the posterior aspect was diffusely but unevenly thickened by tough, pearly-grey tissue forming occasional bosses, up to 0·25 cm. thick, which deformed the adjacent cord. The infiltration was greatest over the lower thoracic segments, diminishing towards the cervical segments and the cauda equina. The arachnoid membrane covering the latter was moderately thickened and in many places adherent to the dura. Its deep surface was studded with minute pinkish-red granulations which gave it a velvety appearance. The lumbosacral nerve roots were often matted together and in places bore moniliform swellings which, however, were less conspicuous than in Case 1. Most of the lumbar roots were accompanied by a cystic dilatation of the subarachnoid space where the root penetrated the dura mater, and immediately proximal to the ganglion. These cysts measured up to 2 by 1·3 by 1 cm. and were lined by velvety granulations similar to those observed over the intrathecal part of the arachnoid membrane.

On transverse section the cord appeared unaltered, with the exception of the 4th thoracic segment where a pinhead white nodule was embedded in the posterior border of the median raphe.

Microscopic.—The material was fixed in 4 per cent. formaldehyde. The technical methods were similar to those used in Case 1.

The nodule in the tuber cinereum is composed of loosely clumped small spheroidal and polygonal cells from 5 to 8 μ in diameter (fig. 8). In some a small quantity of cytoplasm surrounds the nucleus; in others the cytoplasm is expanded by large vacuoles. The nuclei are spherical, contain pale nucleoplasm, 1 to 2 nucleoli and a moderate amount of chromatin evenly disseminated as small nodes. In many places groups of the cells are separated by shreds and irregular masses of a homogeneous coagulum which stains feebly for mucin. No fibrils or blepharoplasts are present in the cells, but a scanty fibrillar neuroglial stroma is present towards the periphery of the nodule. Blood-vessels are few; their adventitia contains occasional macrophages laden with iron pigment.

The nodule does not reach the meninges covering the tuber cinereum, which appear normal, or the optic tracts over which the meninges are thickened by fibrosis and sparsely infiltrated by tumour cells. Dorsally, however, it gains the cavity of the 3rd ventricle by a gap in the ependyma. Small groups of tumour cells are

present in the adjacent lumen, and replace the ependyma in many areas on its ventro-lateral walls.

The ependyma of the right frontal horn is often replaced by confluent plaques and rounded masses of spheroidal cells identical in appearance with those composing the tuberal nodule, and similar to those described in Case 1 (fig. 10). In the occipital horn no tumour cells are present in the ependyma; the latter is, however, replaced in a few areas by low plaques of fibrillar glia. The floor and lateral walls of the 4th ventricle are almost entirely composed of confluent nodules and plaques of sparsely cellular tumour tissue similar to that in the frontal horn. Small groups of engorged capillaries are often present at the surface of the nodules and, in places, the loops project into the lumen of the ventricle. A few small flattened nodules interrupt the ependyma over the roof.

The *cerebral leptomeninges* show a dense fibrosis and cellular infiltration similar to that described in Case 1, but more clearly of a neoplastic character. Thus, large islands of tumour cells distend in places the meshes of the pia-arachnoid, especially in the mouths of the sulci, as shown in fig. 9. A faint mucinous reaction is occasionally demonstrable in the collagenous stroma, especially near the surface of the cortex. As in Case 1, the meningeal reaction is most conspicuous at the base of the brain, but diminishes over the frontal convexities and is absent from the lateral aspects of the occipital lobes. There is no invasion of the cortex by tumour.

Spinal cord: The pia-arachnoid is densely but unevenly thickened by fibrosis. The reaction is greatest in the mid-posterior line and, as in Case 1, diminishes in crescentic fashion over the lateral aspects of the cord. It is greatest in the thoracic segments where it embraces the cord as far as the anterior roots which are focally infiltrated by the tumour cells. The thickened meninges are in general sparsely infiltrated by these cells but, as in the cerebrum, there are conspicuous focal collections in the meshes of the collagen. In the 4th thoracic segment such a collection of cells in the depths of the pia depresses and superficially infiltrates the cord in the mid-posterior line. Apart from this the substance of the cord is unaffected.

The *posterior spinal roots* are conspicuously infiltrated by tumour cells, especially in the cauda equina where the fibres are sometimes widely separated by rows of greatly vacuolated cells (fig. 11). The walls of the cystic expansions on the roots just proximal to the ganglia are composed of fibrotic meninges infiltrated by tumour cells, small lymphocytes and many large monocytes laden with iron pigment. In places the fibres of the roots are incorporated in the wall and are widely separated by the infiltration. The lining of the cysts is composed of arachnoid membrane thickened by the projection from its surface of numerous capillary tufts. A similar vascularization and infiltration of the membrane by tumour cells is present over the cauda equina, accounting for the pink velvety appearance seen with the naked eye. No mucinous reaction was obtained in these spinal tissues.

Comment.

Pathologically and clinically this case is remarkably similar to Case 1. The primary focus here occupied the tuber cinereum and had extended to the 3rd ventricle, permitting the dissemination of tumour cells throughout the cerebrospinal pathway. The neoplastic character of the meningeal infiltration was more obvious both macroscopically and microscopically

than in Case 1, and the reactive fibrosis was less pronounced. These features are doubtless correlated with the shorter course of the illness. As in Case 1 the history was one of epileptiform attacks and headache with, in addition, grave visual failure, difficulty in speech, severe pains in the chest, abdomen and back, and terminal bladder disturbances with spasticity of the lower limbs. The anorexia and inversion of sleep-rhythm are of interest in association with the tuberal lesion discovered on examination of the brain. As in Case 1 the diagnosis was difficult. The length of the history seemed to preclude carcinomatous cerebral metastases, although the general condition of the patient suggested this diagnosis, while the increased pressure and the high protein were consistent with further dissemination throughout the cerebrospinal pathway. The percentage of protein was higher in the lumbar than in the ventricular fluid and this, together with the attacks of pain in the trunk, terminal loss both of bladder-control and of motor power in the limbs, indicated spinal involvement in addition to an intracranial lesion. The blindness of the right eye and partial anosmia on the right were undoubtedly caused by the neoplastic infiltration in the region of the chiasma and orbital surfaces of the frontal lobes.

Case 3.—R. I. 15826. L. C., a schoolgirl, aged 6½, was admitted on June 6, 1941, to the Nuffield Department of Surgery on account of left-sided headaches and right exophthalmos. Six months before she had had measles. Though suffering from frequent colds she continued to do well at school until ten weeks before admission, when she began to have short sharp pains over the right eye two or three times a day. Her sight became impaired and her right eye began to protrude. She also suffered from generalized headaches, at times associated with vomiting. Her character and mood had remained unchanged and there had been no fits.

Examination.—The patient was a normal, healthy-looking, co-operative and attentive child who slept more than normally. Her skull was not appreciably enlarged (51 cm. circumference). Her sense of smell was completely lost. There was bilateral optic atrophy and vision was reduced to appreciation of hand movements in the right eye and $\frac{5}{60}$ in the left, with bitemporal hemianopia. The right eyeball was displaced downwards and forwards to a moderate degree and its movements were slightly limited in all directions. The pupils were dilated and equal and the left reacted to light, the right being inactive.

Radiographic examination of the skull showed widening of the sutures with some erosion of the roof and medial wall of the right orbit, also of the dorsum sellæ and lamina cribrosa. There was a rounded, lightly speckled area of calcification, measuring 5 by 4 cm., in the right frontal lobe, extending diffusely towards the floor of the anterior fossa. Lumbar puncture yielded a clear, colourless fluid at 300 mm. pressure, containing 30 mg. per cent. of protein, whereas the ventricular pressures were 280 mm. with 10 mg. of protein on each side. Ventriculography showed considerable dilatation of both lateral ventricles and of the 3rd ventricle; the right anterior horn was occluded (fig. 2). The 3rd ventricle seemed to be displaced posteriorly although it was exactly in the middle line. There was no further displacement and the foramina of Monro were enlarged.

Operation, June 20, 1941.—Subtotal removal of oligodendroglioma of the right frontal lobe. A right osteoplastic flap was elevated and part of the lobe resected (see description of biopsy specimen). A subcortical, focally calcified glioma was encountered, extending to the wall of the frontal horn, which was opened. A reddish-

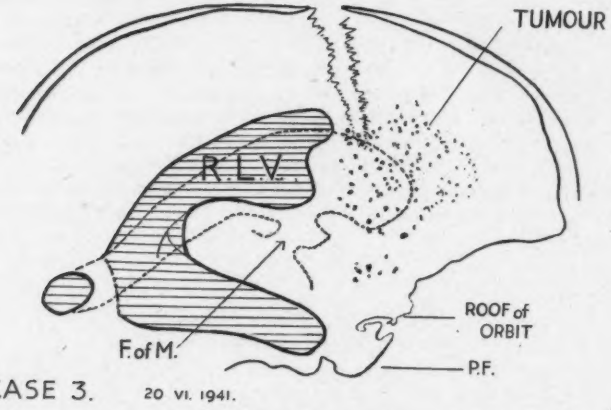

FIG. 2 (*Case 3*).—Tracing of ventriculogram, showing calcification of tumour and filling defect of right anterior horn.

grey nodule of tumour protruded from the inferior aspect of the frontal lobe and was embedded in the wall of the orbit.

Progress.—After operation, yellow fluid collected in the tumour cavity and was tapped on many occasions during the three months of survival. On June 26, six days after operation, she complained of stiffness of the neck. There were, however, no clinical signs of meningitis and no organisms in the cerebrospinal fluid. The protein content of the lumbar fluid rose to 100 mg. per cent. From July 1 she had a complete manometric block. She became drowsy, doubly incontinent and virtually blind. Deep X-ray therapy was without effect. Towards the end of August, some two months after operation, suppuration of the right upper eyelid occurred with extension to the tumour cavity and pyocephalus. She died on September 22, three months after operation.

Pathological examination.—The tissues obtained from operation and necropsy were fixed in 4 per cent. formaldehyde. The staining methods were similar to those used in the preceding cases.

Biopsy specimen.—The specimen consisted of a hemispherical portion of the right frontal lobe, measuring 5 cm. in diameter and up to 3·5 cm. in depth. The meninges and cortex appeared normal, but the deep surface of the white matter was replaced by firm, pearly-grey tumour for a depth of up to 0·7 cm. On section this tissue was subdivided into small lobules by anastomosing opaque yellow strands. Accompanying the specimen were numerous small fragments of similar tumour tissue.

Microscopically the tumour is almost everywhere separated from the white matter by a narrow zone of gliosis in which the cells show evidence of compression. It is composed of compact masses of polygonal cells separated by fairly abundant blood-vessels, most of which are capillaries. The tumour is further subdivided by broad irregular bands of necrotic tissue containing occasional groups of calcified amorphous particles, and infiltrated with lipoid-laden microglial cells. Similar cells often separate smaller groups of the tumour cells. The latter are much smaller, being from 7 to 10·5μ, and contain a spherical nucleus with inconspicuous nucleoli and a moderate amount of chromatin. The cytoplasm is scanty and slightly granular. Some of the cells are greatly ballooned by vacuoles and are then about 15 μ in diameter. They contain neither neuroglial fibrils nor blepharoplasts. Many mitotic figures are present. With Penfield's silver carbonate method for oligodendroglia and microglia they present the characteristic features of oligodendroglial cells and most of the cells are impregnated (fig. 12). A conspicuous mucinous reaction is present in many parts of the stroma, and in the neuroglial tissue separating groups of the cells at the periphery of the tumour. The adjacent cortex and meninges appear normal.

Summary of necropsy (R. I. P.M. No. 482, 1941).

Cardiac failure. Pulmonary congestion. Oligodendrogliomatosis of the cerebrospinal pathway.—Congestion of liver. Slight albuminous degeneration of kidneys. No abnormality in remainder of organs. A well-nourished child.

Examination of central nervous system. Macroscopic.—Brain: Numerous slightly raised pinhead and serpiginous opaque chalky flecks were distributed throughout the dura mater over the cerebral convexities. In freeing the brain about the site of operation in the right frontal region a considerable quantity of slightly cloudy cerebrospinal fluid escaped from the ventricle and the cerebral hemispheres collapsed. The right frontal lobe was fluctuant and was coated, beneath the bone-flap, by a thin layer of pus. Ventral to this was a lobulated mass of soft, milky-white tumour, measuring 7 cm. in diameter, which projected from the brain and encroached upon the left frontal and right temporal poles. It excavated the cribriform plates for a depth of about 2 cm. and extended back to overlap the diaphragma sellæ. The bone adjacent to the tumour was thin and translucent, but there was no evidence of extension of the neoplasm beyond the confines of the skull. The dura covering the bone was, however, extensively infiltrated, especially over the right orbital plate, and nodules of growth projected from the tentorium cerebelli. The basal cisterns were filled with soft white tumour which formed a continuous nodular layer over the brain-stem, obscuring the nerve roots. A thinner layer extended over the temporal poles, the Sylvian fissures and the lateral aspect of the left hemisphere. An interrupted layer of tumour covered the greater part of the cerebellum and occipital lobes.

On section the tumour in the right frontal lobe replaced the floor of the adjacent ventricular horn. A few silver clips were identified in the neighbourhood. The right lateral ventricle was enormously expanded, its ependyma being for the most part coated with fibrino-purulent exudate. The remainder of the ventricular system was also expanded and contained similar exudate. The ependyma in the temporal and occipital horns bore a few nodules of tumour, measuring up to 1·5 by 0·5 by 0·5 cm., and some similar nodules were present in the walls of the 4th ventricle. The velum interpositum was conspicuously infiltrated with tumour.

Spinal cord: A continuous layer of tumour, up to 0·3 cm. thick, occupied the subarachnoid space throughout the length of the spinal cord and formed nodules,

up to 1 by 0·6 by 0·5 cm., on the roots of the cauda equina. The substance of the cord was not macroscopically altered.

Microscopic.—The tumour everywhere shows the same characters as in the earlier biopsy specimen except that the silver impregnations for oligodendroglia were unsuccessful. The recurrence in the right frontal lobe appears to occupy the meninges, including the dura, rather than the brain itself, and contains an abundant connective-tissue stroma which gives a strongly mucinous reaction especially near the cortex. In many areas the mucinous stroma is so abundant that short strings and small groups of the cells are widely separated. The interstices of the marginal glia are sometimes distended with a similar mucinous coagulum.

Sections from the left temporal and right occipital lobes show diffuse, massive infiltration of the leptomeninges with tumour of similar character. There is much mucin in the stroma and a considerable production of reticulum fibres supporting nests of the tumour cells (fig. 13). The cortex shows focal invasion by broad wedges and nodular masses of tumour, but very little infiltration of the sheaths of the perforating vessels.

The meningeal infiltration is intenser in the posterior fossa, especially over the brain-stem where the cranial nerves are, in places, diffusely infiltrated by tumour cells. The cortex of the cerebellar folia near the brain-stem is in places destroyed through diffuse invasion by tumour (fig. 14), but the folia of the lateral lobes often contain circumscribed masses of growth forming pale areas in the depths of the cortex and subjacent white matter large enough to be seen in the stained preparations with the naked eye.

The *ependyma* of the right occipital horn is replaced in many areas by a thick exudate of neutrophil leucocytes, plasma cells and lymphocytes mingled with tumour and foam-cells. This infiltration, supported by fibrin filaments, forms a thick layer over the surface of the ependyma and extends into the subependymal glia where the vessels have undergone proliferation and are cuffed with the infiltrating cells. Over the left pulvinar the ependyma is replaced by irregular well-defined masses of tumour cells, forming bosses up to 0·7 cm. deep. The tufts of choroid plexus opposing this appear normal, but the villi that project towards the cavity of the ventricle are coated with a thick layer of fibrin and a young granulation tissue densely infiltrated with plasma cells, lymphocytes and sparser neutrophil leucocytes. There is slight infiltration of the stroma of the plexus by these cells.

The subarachnoid space of the *spinal cord* is occupied by a thick continuous layer of closely packed tumour cells which also infiltrate the pia, the spinal nerve roots and, to a slight extent, the margins of the cord. The sheaths of a few perforating vessels are also slightly infiltrated. Lymphocytes are present in the meningeal infiltration but are greatly outnumbered by the tumour cells.

Sections of the hinder part of the *right orbit* and *cribriform plate* show marked erosion and atrophy of the bone without neoplastic invasion. The dura is greatly thickened by infiltration with tumour cells and an increase of collagen fibres. The sheath of the right optic nerve is greatly expanded by tumour, but the nerve itself shows no change beyond degeneration of the myelin sheaths (fig. 15).

Comment.

The initial malignancy of the tumour in this case, a classical example of oligodendroglioma, was indicated by the numerous mitotic figures in the biopsy specimen. There can be little doubt that active dissemination

of the tumour cells followed operation through access to the frontal horn, but pre-operative evidence of ventricular dilatation suggests that a considerable spread had already taken place, though in this connection it must be noted that there was at this time no rise of protein in the cerebrospinal fluid.

In the macroscopic features of the metastasis through the cerebrospinal pathway the tumour resembled the medulloblastomas and retinal gliomas of early childhood; this agreed with the fulminating clinical course as compared with that in Cases 1 and 2. Cytologically, however, the glioma was unquestionably composed of oligodendroglial cells. A remarkable feature was the pronounced mucinous alteration of the stroma, both in the primary tumour and in the infiltrated leptomeninges. Again, the mesodermal reaction in the meninges with production of reticulum fibres was greater than is usually seen in the most malignant gliomas.

The insignificant enlargement of the child's skull in association with such a large tumour suggests a rapid course. Both lumbar and ventricular pressures were high before operation although in this case, unlike the others, the protein content of both fluids was at first normal. This was the only case in the series in which spinal manometric block was observed, and it occurred shortly after operation. It is to be correlated with the continuous layer of tumour occupying the spinal subarachnoid space. The post-operative infection prohibits any dogmatic interpretation of the rise of protein noted before there was either clinical or bacteriological evidence of this complication.

Case 4.—R. I · 7158. C. B., a girl, aged 4, was admitted to the Nuffield Department of Surgery on March 6, 1940, on account of headache, vomiting, pains in the limbs and dragging of the right leg. Seven months previously the child had suffered a minor head injury without loss of consciousness. One month after this it was noticed that her head was increasing in size. However, she remained well until two months before admission, when she began to drag her right leg and complained of pain in her right thigh. She became increasingly tired, listless and irritable, with occasional headaches and vomiting. Her gait grew more unsteady. Although her appetite remained good she lost weight. A few days before admission the pains in her legs became so intense that she would not extend them. She had never had fits or lost consciousness.

Examination.—The child lay in a flexed position. She looked rather ill and rapidly became fatigued. Intelligence was normal and she had no manifest speech defect. Her head measured 54 cm. in circumference (normal, 50 cm.) and gave a cracked-pot sound; the veins of her forehead were dilated. She had no anosmia. Details of pictures were recognized with each eye. The fundi showed bilateral papilloedema of 3 to 4 dioptres with marked venous engorgement. The pupils were

PLATE IX.

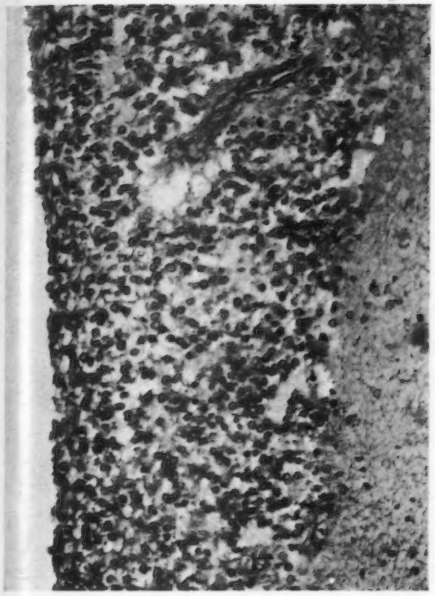

FIG. 3.

FIG. 4.

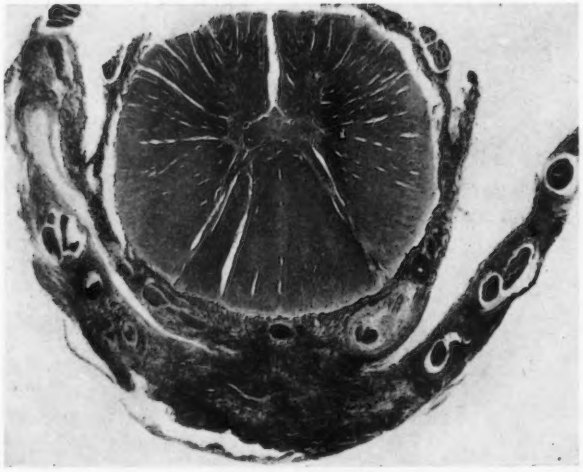

FIG. 5.

To illustrate article by Diana J. K. Beck and Dorothy S. Russell.

PLATE X.

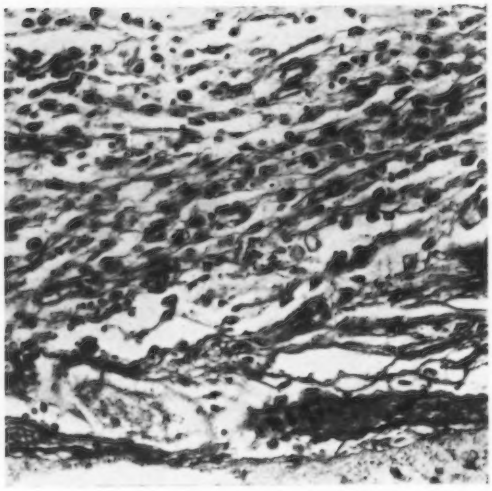

FIG. 6.

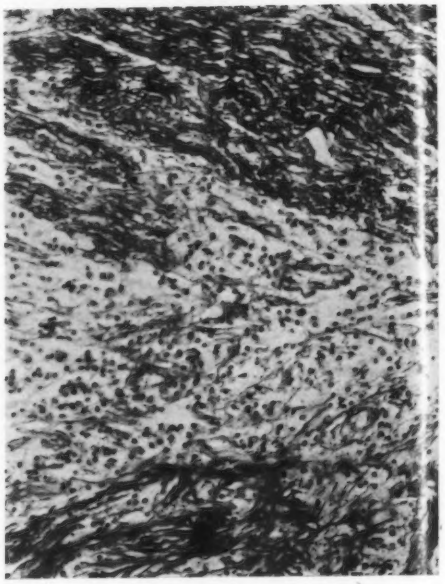

FIG. 7.

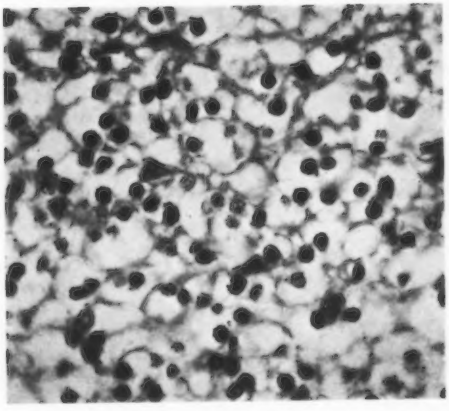

FIG. 8.

FIG. 9.

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PLATE XI.

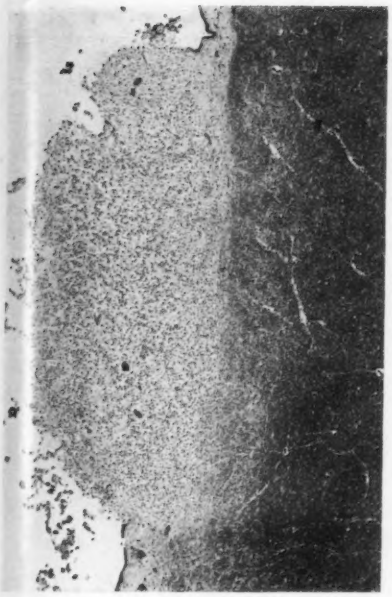

FIG. 10.

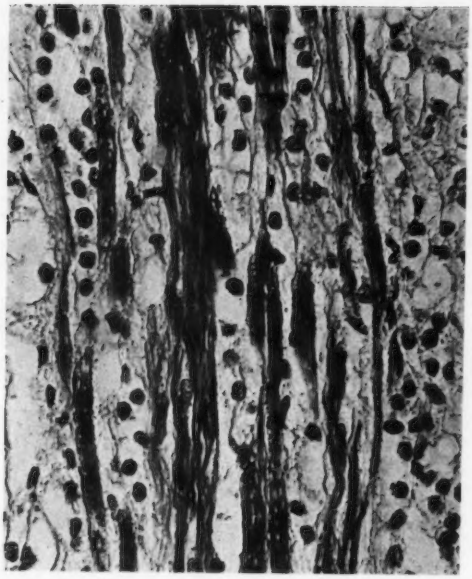

FIG. 11.

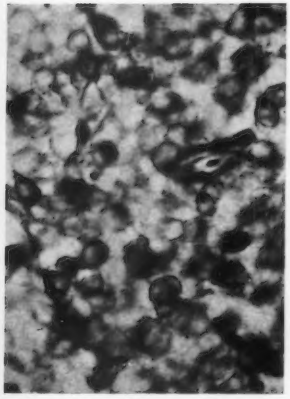

FIG. 12.

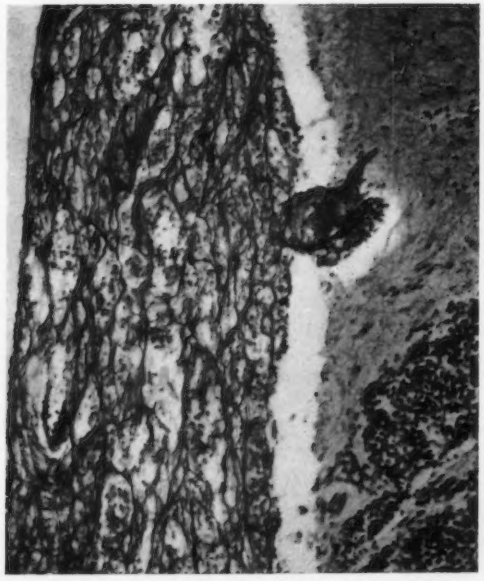

FIG. 13.

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PLATE XII.

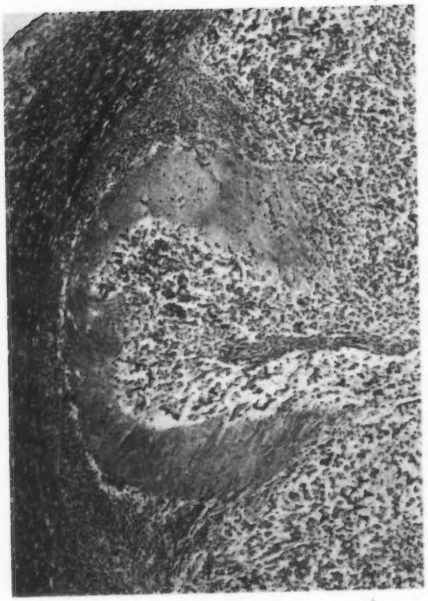

FIG. 14.

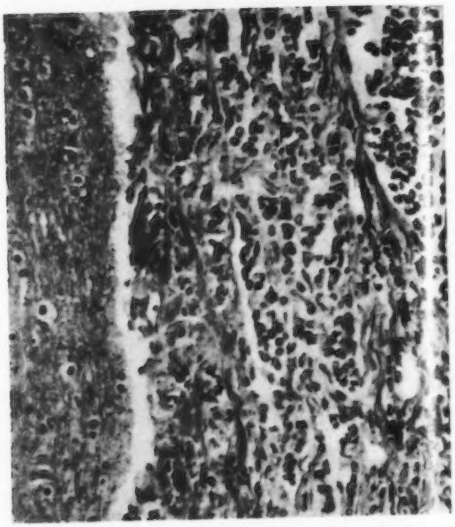

FIG. 15.

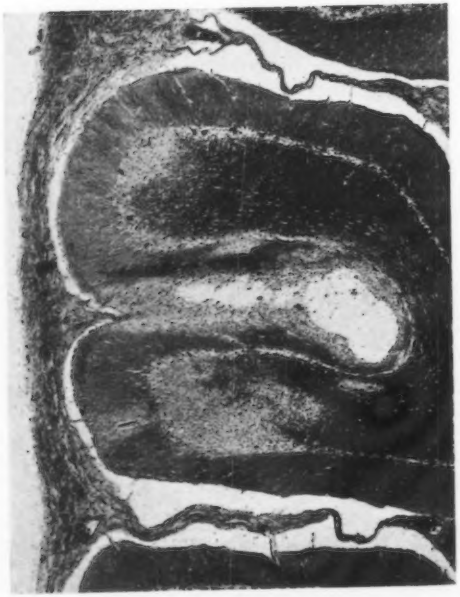

FIG. 16.

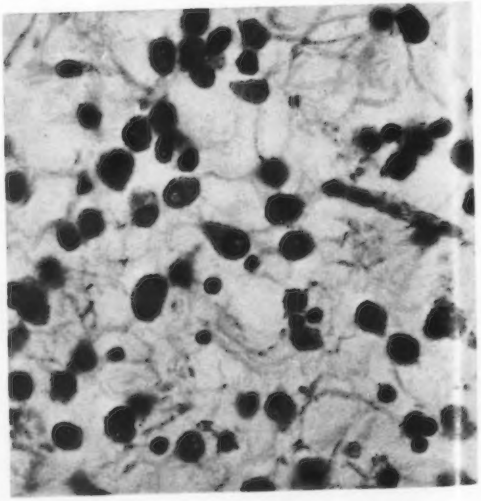

FIG. 17.

To illustrate article by Diana J. K. Beck and Dorothy S. Russell.

moderately dilated, equal and reactive. She had moderate weakness of the right lower face, and of the right arm and leg. The tone was increased in the legs, especially in the right. Tendon-jerks were increased in the right arm and diminished in the legs. The right abdominal reflexes were diminished and the right plantar was extensor, the left flexor. Sensibility appeared to be normal.

Radiographic examination of the skull showed spreading of the sutures. Lumbar puncture yielded clear, colourless fluid under 450 mm. pressure and containing 200 mg. per cent. of protein with 2 lymphocytes per c.mm. The ventricular pressure was 400 mm.; the fluid was clear and colourless and contained 100 mg. per cent. of protein on the left and 90 mg. on the right. Ventriculography on March 14 showed dilatation of the ventricles, which was greater on the left than on the right, with a little irregularity of the outline of the 3rd ventricle. There was a filling defect in the lower part of the 4th ventricle. These appearances, together with the raised protein, suggested metastatic deposits.

Progress.—Ventriculography was followed by severe headache and an opisthotonic attack in which the child was deeply unconscious, with depressed respiration. Ventricular puncture effected relief, but it was ten days before she began to respond properly, by which time she had become virtually blind. Deep X-ray therapy was without beneficial effect. Within two months all the limbs, except the right upper limb, showed a gross flaccid paresis and loss of tendon-jerks. Her right upper limb was weak and spastic and its tendon reflexes were present. Her neck was stiff and there was a positive Kernig sign. She was taken home on May 19, 1940, and died ten days later.

Necropsy.—A post-mortem examination was made by Dr. Leonard Lancaster, who kindly sent us the brain hardened in formalin for further examination, with a report that no important changes had been observed in the other organs. The spinal cord was not examined.

Examination of brain. Macroscopic.—The ventricles had collapsed during fixation of the brain, with consequent gross deformity. A conspicuous milky-white thickening affected the leptomeninges throughout the base, the hippocampal gyri, orbital surfaces of the frontal lobes and ventral surface of the cerebellar hemispheres. It was less marked over the ventral aspect of the occipital lobes, the dorsal surface of the cerebellum and diminished further over the cerebral convexities, where the sulci only were affected. In both parieto-occipital regions the meninges were thin and transparent. Each olfactory bulb was expanded by homogeneous white tumour tissue and measured about 1·5 by 0·8 by 0·4 cm. A nodule of similar tissue, 0·5 cm. in diameter, occupied the ventrolateral border of the left side of the optic chiasm. Sections displayed a diffuse infiltration of the cerebellar and cerebral sulci by homogeneous creamy-white tissue which extended into many parts of the cerebellar folia to form translucent white nodules up to 0·8 cm. in diameter. The ventricles were collapsed and their ependymal lining appeared smooth and corrugated, but without evidence of tumour deposits. There was considerable destruction by post-mortem softening of the region of the septum pellucidum, but the cavum had evidently been widely patent during life. The pineal body was not found. Close search failed to disclose any mass of tumour of greater size than those already described.

Microscopic.—Cerebellum: There is gross fibrous thickening of the leptomeninges in most places over the summits of the folia, but it is less marked and sometimes absent in the sulci. This is accompanied by a diffuse, often sparse, infiltration by small polygonal cells from 7 to 9 μ in diameter, which tend to form clumps

and short trabeculæ amongst the collagen fibres. Some of the cells are larger, measuring up to 14 or rarely 25 μ. Each cell has a spherical, usually eccentric nucleus with a fairly thick nuclear membrane, and a dusky or lightly stained nucleoplasm containing fairly abundant fine and coarse chromatin nodes and 1 or 2 inconspicuous nucleoli. The cytoplasm is slightly granular and has ill-defined, fluffy borders with occasional short tapering processes. No fibrils or blepharoplasts are present. Amongst these cells are a few spindle fibroblasts but no cellular inflammatory reaction. Towards the surface of the cortex these small tumour cells are often mixed with fibrillary astrocytes of pilocytic type which appear to be derived from the marginal glia. These sometimes form a tangential layer on the deep aspect of the pia. No mucinous changes were observed in the stroma of the meninges.

At many points the cortex is replaced by broad tongues of somewhat rarefied neuroglial tissue containing sparse tumour cells forming well-defined pale areas visible to the naked eye in stained preparations. These areas of infiltration are often independent of the perforating vessels and tend to expand in the granule-cell layer producing nodules that may, in section, appear to be confined to this layer (fig. 16). The cells in these foci are similar to those in the meninges (fig. 17), but more often have a bulky vacuolated cytoplasm. They are separated by a mucinous stroma in which fibrillary astrocytes are sparsely and evenly distributed. With Penfield's method for oligodendroglia and microglia the tumour cells in places present the characteristic appearances of oligodendroglial cells, but many are not impregnated. Some preparations made by Dr. del Rio-Hortega, using the double impregnation technique, display the morphological features of the cells in the cortical nodules.

The *tumour in the optic chiasm* abuts on the pia and presents histological features identical with the cerebellar nodules. There is gross fibrous thickening and sparse neoplastic infiltration of the adjacent meninges. The ependyma of the 3rd ventricle is missing in many places but there is no evidence of tumour either here or in the lateral ventricles.

The *leptomeninges over the left frontal lobe* are greatly thickened by fibrosis and sparsely infiltrated with tumour cells. The adjacent cortex is superficially infiltrated in a few places by broad shallow wedges of sparsely cellular tumour tissue. Elsewhere the Virchow-Robin space in a few of the perforating vessels contains a thin sleeve of tumour cells.

Over the *left occipital lobe* the fibrosis is patchy and chiefly affects the sulci. Near such areas the superficial cortex is occasionally infiltrated by narrow wedges of tumour.

Comment.—In the chronicity of the meningeal reaction and degree of infiltration of the subjacent brain this case is intermediate between Cases 1 and 2 (most chronic) and Case 3 (fulminating). Clinically it was regarded as a right hemisphere tumour with spinal metastases until ventriculography showed bilateral hydrocephalus which suggested a cerebellar medulloblastoma with diffuse metastatic deposits.

Macroscopically the appearances in the brain resembled those of a medulloblastoma. But histologically the tumour cells proved to be oligodendroglial. There was no obvious primary tumour unless the nodule in the optic chiasm can be so regarded. It was in contiguity with the meninges and the possibility that it formed part of the secondary

spread cannot be excluded, for it was no larger than many of the cerebellar foci. It is regrettable that the spinal cord was not examined, since the primary focus might have been at this level, especially as limb pains were an early symptom. There can be little doubt that the pains, the weakness with fixed flexion and the loss of reflexes of the limbs were due to involvement of the spinal roots by neoplasm. The increased protein in the lumbar fluid supports this interpretation.

Discussion.

In these four cases a diffuse spread of oligodendroglioma took place throughout the subarachnoid spaces, including those of the spinal cord in the three examples in which this was examined. The primary tumour abutted on the ventricular system in all except Case 4, and then was associated with ependymal deposits. In Cases 1 and 2 the primary tumour was very small. In Case 4 the ependyma was not involved, although the ventricular protein was high, and the site of the primary tumour was uncertain.

Dissemination of the tumour cells was spontaneous though it was probably accelerated by operative interference in Case 3. But in this case ventriculography revealed dilatation of the ventricles, including the third, before operation; it may therefore be inferred that meningeal deposits were already present at this time.

Certain distinctions may be drawn between the clinical course and pathology of the two adults on the one hand, and those of the children on the other. In the latter (Cases 3 and 4) the shortness of the clinical history and the macroscopic appearances of the meninges were reminiscent of medulloblastoma. In the adults (Cases 1 and 2) the history was longer and the macroscopic changes in the meninges strongly suggested, especially in Case 1, a chronic arachnoiditis of unknown ætiology. The length of the clinical history is in fact directly proportional to the degree of meningeal fibrosis in the four cases. In Case 1 both were maximal. If histological examination had been confined to the meninges in this case it is doubtful whether the true nature of the "arachnoiditis" would have been determined, and it may be that similar cases have escaped elucidation in the past. Thus, it is of interest that Davis and Haven (1931), in their report of a series of cases of chronic arachnoiditis, record their suspicion that some, in which pathological examination was limited to a biopsy of the arachnoid membrane, were perhaps of a neoplastic character.

The oligodendrogliomas may thus vary widely in their behaviour. They may proliferate as actively as any of the more malignant gliomas, as shown in Cases 3 and 4; on the other hand the metastases may undergo little active growth, promoting rather a meningeal fibrosis as in Cases 1 and 2.

Again it is possible that similar cases have masqueraded in the past as "diffuse sarcomatosis" since this diagnosis, according to Ford and Firor (1924), rested to a large extent histologically on the absence of neuroglial fibres in the tumour cells. In retrospect Ford and Firor's first two cases of "sarcomatosis," in which a primary intraventricular tumour was demonstrated, must almost certainly have been gliomas. In their first case the size and position of the tumour was almost identical with those in our Case 1.

A point of diagnostic importance histologically is the presence of a diffuse mucinous change in the stroma in these oligodendrogliomas. This was conspicuous in Cases 3 and 4, but slight in the others. It is a recognized degenerative change in oligodendroglial cells in general (Bailey and Schaltenbrand, 1927) and has been noted as an important feature in tumours of these cells by Greenfield and Robertson. A special search for mucin in other examples of metastasizing gliomas, including three medulloblastomas, one neuroepithelioma of the retina and five spongioblastomas failed to reveal any, except a trace in the neuroepithelioma.

A variable degree of hydrocephalus occurred in all our cases in association with persistently high intraventricular and spinal fluid pressures, and was also noted in their cases by Ford and Firor (loc. cit.). The fluid had a high protein content, probably due in part to spontaneous hæmorrhage. This may have originated in the capillaries which abounded in places at the surfaces of the ependymal nodules. A similar distribution of vessels was described by Hasenjäger (1939) in the "ependymitis blastomatosa" associated with spongioblastoma multiforme. In the final stages of Case 1 the bleeding increased with successive ventricular tappings. In Cases 1 and 4, however, a raised protein was observed at times without any evidence of hæmorrhage; the latter therefore was not entirely responsible for the increased protein as a whole. In view of the extent of the metastases it is remarkable that so few cells were recorded in the spinal fluid in our cases. Those seen were usually identified as lymphocytes; in retrospect they may in fact have been tumour cells since lymphocytic infiltration was nowhere a prominent histological feature.

With so extensive an infiltration of the base of the brain, particularly in

Case 3, the clinical evidence of cranial nerve involvement is remarkably scanty. Vision, however, was virtually destroyed without much antecedent papillœdema in Cases 2 and 3. In these and in Case 4 the discs eventually showed secondary atrophy, and this was undoubtedly due to infiltration of the optic nerves. In Cases 3 and 4 loss of sight occurred rapidly; in Case 2 it was for a time unilateral. The complete anosmia in Case 3 and partial in Cases 1 and 2 is explained by infiltration of the olfactory bulbs and tracts. Again, there was little objective evidence of spinal nerve involvement, though subjective sensory disturbances were recorded in Cases 1, 2 and 4 and were in all probability the result of infiltration of the posterior roots. The triviality of spinal symptoms was also noted by Ford and Firor in "sarcomatosis," and by Cairns and Russell (1931) in gliomatous metastases in general. The explanation probably lies in the tendency of the tumour cells to separate the nerve fibres rather than destroy them.

In the children (Cases 3 and 4) the clinical symptoms as a whole present no features that distinguish the cases from other varieties of diffuse meningeal neoplasm in children. But in the two adults there was a long history of focal epilepsy, convulsive attacks and mental disturbance without any signs indicating a progressive focal lesion. The gustatory, olfactory and visual hallucinations in these cases may be explained by the deposits of tumour in the basal meninges, although it is possible that they were produced by variations in the degree of hydrocephalus. Considerable remission of symptoms was recorded in Case 1 although the hydrocephalus was progressive.

The failure of deep X-ray therapy to confer any benefit in Cases 1, 3 and 4 accords with the growing view that the oligodendrogliomas, as a class, are not susceptible to this form of irradiation in contrast to the behaviour of medulloblastomas.

Summary.

Four cases are reported in which an oligodendroglioma formed metastases throughout the cerebrospinal pathway.

Two of the cases were in adults, and in these the clinical course was prolonged while the macroscopic appearances of the central nervous system resembled those commonly referred to as "chronic arachnoiditis."

The other two cases were in children; in these the clinical course was rapid and the macroscopic appearances of the metastases suggested a highly malignant glioma such as medulloblastoma.

We wish to thank Mr. D. W. C. Northfield for permission to use the clinical notes in Case 2, and Dr. A. H. T. Robb-Smith for the necropsy summaries in Cases 1 and 3.

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LIST OF FIGURES.

FIG. 3 (*Case 1*).—Septum pellucidum showing replacement of ependyma by layer of oligodendroglial cells. P.T.A.H. × 180.

FIG. 4 (*Case 1*).—Longitudinal section of lumbar root showing degeneration of fibres in border of neoplastic infiltration. Spielmeyer. × 15.

FIG. 5 (*Case 1*).—Thoracic cord showing thickening of arachnoid and pia. P.T.A.H. × 7.

FIG. 6 (*Case 1*).—Leptomeninges from orbital surface of frontal lobe thickened by fibrosis and neoplastic infiltration. P.T.A.H. × 170.

FIG. 7 (Case *1*).—Nodule on lumbar root showing neoplastic infiltration (centre), nerve fibres (above) and coarse collagen fibres (below). P.T.A.H. × 180.

FIG. 8 (*Case* 2).—Cells in primary tumour in tuber cinereum. H. & E. × 390.

FIG. 9 (*Case* 2).—Frontal lobe showing neoplastic infiltration of meninges in mouth of sulcus. H & E. × 170.

FIG. 10 (*Case* 2).—Frontal horn showing replacement of ependyma by mass of tumour cells. H & E. × 26.

FIG. 11 (*Case* 2).—Posterior lumbar root showing separation of nerve fibres by vacuolated tumour cells. P.T.A.H. × 440.

FIG. 12 (*Case* 3).—Primary tumour (operation specimen) showing characteristic appearance of cells with silver carbonate. Penfield's combined method. × 480.

FIG. 13 (*Case 3*).—Abundant reticulum fibres in leptomeninges of parietal region with group of tumour cells in meshes. The underlying cortex is invaded by tumour in bottom right-hand corner. Silver carbonate. × 120.

FIG. 14 (*Case 3*).—Region of flocculus showing diffuse invasion and destruction of cerebellar cortex by tumour. P.T.A.H. × 38.

FIG. 15 (*Case 3*).—Infiltration by tumour of sheath of right optic nerve. P.T.A.H. × 220.

FIG. 16 (*Case 4*).—Cerebellum showing thickening of meninges and infiltration of molecular and granular layers of cortex (pale areas). P.T.A.H. × 25.

FIG. 17 (*Case 4*).—Cells in nodule of cortical infiltration in cerebellum widely separated by mucinous stroma. Silver carbonate. × 660.

FUNCTIONAL RECOVERY FOLLOWING NERVE GRAFTS AND OTHER TYPES OF NERVE BRIDGE.

BY E. GUTMANN AND F. K. SANDERS[1]
Department of Zoology and Comparative Anatomy, Oxford.

Introduction.

In previous papers (Sanders, 1942, Sanders and Young, 1942) it has been shown that it is possible to divide nerve grafts into (*a*) *incorporated grafts* which survive and are incorporated into the tissues of the host, providing Schwann tubes down which the new fibres can grow, such as autografts and stored and fresh homografts, and (*b*) *replacement grafts*, which are replaced by the tissues of the host, the replacing tissues providing a bed for the outgrowth of new fibres and Schwann cells from the central stump of the cut nerve, and of Schwann cells from the peripheral stump.

There are reasons for believing that "incorporated" grafts are likely to be followed by a better sensory and motor recovery than "replacement" grafts. They are more rapidly and profusely innervated. Moreover, the course of outgrowth of a nerve fibre being presumably directed by surface forces (Weiss, 1941), the orientated Schwann bands of an incorporated graft form a better means of directing the new fibres in parallel columns than the haphazardly arranged macrophages in the tissues which take the place of a replacement graft. Thus less deviation and shunting of fibres is likely to take place in an incorporated than in a replacement graft.

Recovery of both sensory and motor function in animals has been reported by various workers following all types of nerve graft (*see* Sanders, 1942). But the defect of the entire experimental and clinical literature is that no standard test of recovery of function has been applied to the results of different grafts. Sanders and Young (1942) have attempted to compare the various types of graft by estimating the distances to which new pain fibres grow through the grafts after short periods of time, and by comparison of the histological condition at these times. Such criteria are of course in many ways inferior to the test of functional recovery, although they enabled the distinction between incorporated and replace-

[1] Harmsworth Senior Scholar, Merton College.

ment grafts to be made, and demonstrated a superiority of autografts over the other types.

The experiments described in this paper represent an attempt to compare the efficiency of various types of nerve graft by means of standard tests of functional recovery. This has been done (1) by estimating the time of onset and amount of recovery after different grafts made into a mixed nerve (peroneal) of a specific reflex (toe-spreading reflex) in muscles innervated by that nerve; (2) by studying the changes in extent of the skin area left analgesic after severance of this nerve; and (3) by comparison of the histological conditions of the various grafts at different times after operation and recovery. The functional results obtained in this way have been compared on the one hand with the results of end-to-end suture, and on the other with the results of the unaided union of stumps across a nerve gap, chosen as being procedures with the best and worst prognosis for recovery following nerve severance. Thus the functional results of the following procedures have been compared: (1) Unaided union of stumps; (2) end-to-end suture; (3) autografts; (4) fresh homografts; (5) homografts stored in Ringer's solution at 2° C.; (6) dead grafts of alcohol-fixed nerve. Fresh heterografts, and grafts of alcohol-fixed spinal cord (Gosset and Bertrand, 1938) have not been investigated. Sanders and Young (1942) found that alcohol-fixed grafts were replaced by a bed of macrophages through which the new outgrowths were able to proceed without conspicuous difficulty. Fresh heterografts were accompanied by an enormous small cell reaction, and grafts of alcohol-preserved spinal cord were enclosed by a capsule of connective tissue, both of which reactions would tend to obstruct outgrowth from the stumps. Thus alcohol-fixed nerve grafts were chosen as the best type of replacement graft, and their results compared with those of incorporated grafts.

Methods

Operative technique. The animals used were adult rabbits of both sexes and of different races, weighing 3 to 5 lb. In an initial aseptic operation under anæthesia (nembutal and ether) the peroneal and tibial nerves were exposed in the thigh of each rabbit, separated, and one of the procedures listed above performed upon the peroneal nerve. In the study of unaided union of stumps a gap of length 2 cm. was made by resecting a segment of the nerve. End-to-end sutures were made according to the technique described by Young and Medawar (1940). The peroneal nerve was cut, and the stumps held together by gripping the epineurium at the side of both stumps with fine watchmakers forceps. The stumps were then stuck together by means of a drop of a solution of cockerel plasma containing an excess of dissolved fibrinogen. When this had clotted, the forceps were removed. In this way firm junctions with a minimum of retraction were obtained. The nerve grafts used were

of a standard length of 2 cm. and were used to fill gaps in the peroneal nerve. The gap in the nerve was made slightly less than 2 cm. in length so that no retraction was likely to take place at the proximal and distal junctions of the graft, and standard junctions were thus obtained. The grafts were fixed in place with cockerel plasma, each junction being made separately. As noted by Sanders and Young (1942), these solutions proved very convenient for the fixing of grafts.

Autografts were made by removing a 2 cm. length of tibial nerve from one side of a rabbit, and using it to fill a gap in the peroneal nerve of the opposite side; homografts by removing a 2 cm. length of tibial nerve from one animal and using it to fill a gap in one of the peroneal nerves of a second animal. In practice, a single donor animal was used to provide grafts for 2 or 3 host animals, and then sacrificed. In the case of stored homografts, large pieces of tibial nerve were taken from a donor animal and stored in sterile Ringer's solution at 2°C. by the technique described by Sanders and Young (1942). After seven, fourteen, or twenty-one days storage in this way 2 cm. pieces of these stored nerves were used to fill gaps in the resected peroneal nerves of host rabbits. Alcohol-fixed grafts were also taken as described by Sanders and Young (1942), Ringer-washed pieces of alcohol-fixed nerve 2 cm. long being used.

Grafts were normally placed on one side only of each rabbit, although in three experiments grafts were placed on both sides. In the bilateral experiments autografts were compared directly with end-to-end sutures, fresh homografts with stored grafts, and stored grafts with alcohol-fixed grafts. Where a direct comparison between autografts and end-to-end sutures was made, the grafts used consisted of 2 cm. lengths of the median nerve. It was impossible to use the standard tibial nerve graft described above since it was necessary to maintain identical conditions of nerve injury on the two sides of the animal, only the peroneal nerve being damaged.

In order to avoid variability in the times of onset of functional recovery in different animals owing to differences in the distance travelled by the new fibres growing down the peroneal nerve, the central stump in unaided unions, the suture line in end-to-end sutures, and the proximal junction in all grafts, was made at a standard distance from the point of entry of the nerve into the peroneus longus. This muscle entry is a convenient fixed point as it is the first motor branch given off by the nerve in its downward course. The distance chosen was 80 mm., as this is approximately the distance from the point at which the peroneal nerve, in its normal course in a medium-sized rabbit, crosses the border between adductor magnus and vastus medialis, to its point of entry into the peroneus longus. The distance was measured roughly on the surface of the skin at operation, and was checked by direct measurement along the nerve at biopsy. Between different animals the distance from central stump to muscle never varied more than 5 mm.

Estimation of motor recovery.—Motor recovery was detected by almost daily examination of the toe-spreading reflex (*see* Gutmann, 1942), which is produced by the peronei I-IV, innervated by the peroneal nerve. This movement is a thoroughly reliable criterion of recovery in the denervated muscle. Moreover degree of recovery can be estimated by plotting the amplitude of spreading upon an arbitrary scale—*the spreading index*, in which Grade 1 represents a mere flicker of response in the 4th toe, Grade 2 just visible spreading of the second, third and fourth toes,[1] Grade 3 some spreading of all these three toes, but with an amplitude less than that elicitable

[1]Spreading of the first toe is performed by abductor hallucis, innervated by the tibial nerve (*see* Gutmann, 1942).

in the normal animal, and Grade 4 full spreading of all three toes with an amplitude equal to normal (*see* Gutmann, 1942).

Estimation of sensory recovery.—Immediately after severance of the peroneal nerve of the rabbit, the whole dorsum of the hind foot and the exterior surface of the leg as far up as the crista tibiæ becomes analgesic. Guttmann and Gutmann (1942), by means of experiments in which the peroneal of the rabbit was cut and regeneration prevented by turning aside the central stump, showed that the part of the peroneal area which lies proximally to a line connecting the two malleoli is a zone of overlap between the peroneal and the surrounding nerves. Thus the only reliable sign of sensory recovery by regeneration in the peroneal nerve of the rabbit is progressive diminution of the area of analgesia on the dorsum of the foot, which is the "autonomous zone" of the peroneal nerve (*see* Guttmann and Gutmann, 1942).

In the present experiments the analgesic areas on the legs of the rabbits were explored with a needle every two weeks following operation, and their boundaries marked with indian ink. Progressive retreat of the line of analgesia along the dorsum of the foot from the malleolar line towards the toes was taken to indicate sensory recovery by regeneration in the peroneal nerve. Histological studies have shown that full confidence may be placed in the results of such tests in the rabbit (Weddell, Guttmann and Gutmann, 1942).

Observations at biopsy.—After operation the animals were kept alive for a maximum period of 200 days. At either this time, or at one of various earlier times, the animal was sacrificed, being opened under light anæsthesia, and the functional result checked by stimulation of the nerve. The stimulus was provided by a faradic coil, using bipolar silver electrodes. After this had been done, pieces of the graft, the host nerve, and the peroneus longus muscle were removed and fixed for sectioning and staining by various methods. These methods were the Bodian silver proteinate and Bielschowsky-Gros for axons in nerve and muscle respectively, the Kulschitzky-Pal for myelin and the Masson trichrome stain for other structures.

Unaided Union of Stumps.

Motor recovery.—The functional results of the closure of two cm. gaps in the peroneal nerve by means of the unaided union of stumps were studied in six rabbits. The results of those experiments are given in Table I and Text-figure I.

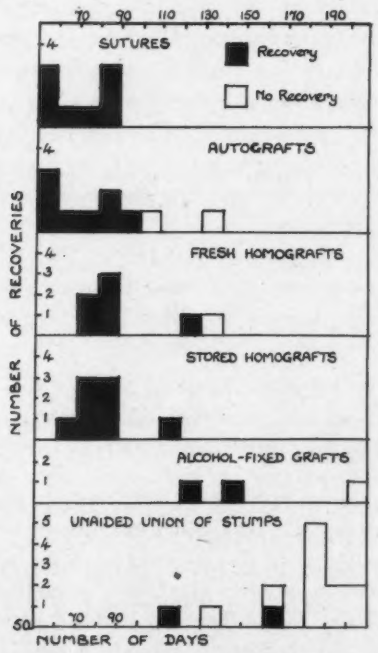
Table I.—Recovery of Function following the Unaided Union of Stumps in the Peroneal Nerve. Summary of Data.

		Motor recovery (spreading)		*Recovery: electrical excitability*				
Animal	*Gap*	*Time of onset*	*Final grade of spreading*	*Time*	*d.f.*	*prn.*	*sprdn.*	*Sensory recovery*
582	20 mm.	117 d.	2	(*a*) 120 d.	−	−	+	None in 180 d.
				(*b*) 180 d.	+	+	+	
581 583 595 596 597	20 mm.	None in 180 d.	0	No visible rejunction of stumps				None in 180 d.

d.f.=dorsal flexion, prn.=pronation, sprdn.=spreading of the toes, d.=days.

Recovery of the spreading reflex only occurred in one out of the six animals with peroneal nerve gaps, minimal spreading of the fourth toe (Grade 1) first appearing 117 days after operation. During the next three weeks there was improvement in the amplitude of spreading elicited, and it finally corresponded to Grade 2 of the spreading index described above (*see* Text-figure 2). No further improvement occurred although the animal was kept alive for 180 days.

All the animals with peroneal nerve gaps were reopened 180 days after operation. Only in the one case which showed motor recovery (animal 582) was any reunion of stumps visible macroscopically. The central stump of the peroneal nerve bore a neuroma from which ran a greyish strand of tissue, connecting it with a fan-shaped proliferation of similar



TEXT-FIG. 1.—Histograms to show the times of onset of motor recovery (spreading) after end-to-end suture, various nerve grafts, and the unaided union of stumps. Grouped by ten-day intervals.

appearance growing from the tip of the peripheral stump (*see* Plate XIII, fig. 1). Reunion appeared to have taken place in the manner already

described by many authors (e.g. Kirk and Lewis, 1917, Young *et al.*, 1940). The five cases in which motor recovery failed all showed neuromatous central stumps and peripheral stumps with proliferations, but in no case was any tissue visible connecting the stumps.

The single peroneal case which showed recovery of reflex movement (animal 582) was reopened by means of an aseptic operation under light anæsthesia 120 days after operation, i.e. three days after motor recovery had begun, and the peripheral stump was stimulated electrically to check whether motor fibres had indeed reinnervated the paralysed muscles. Whatever the voltage used the only movement elicited was weak abduction of the fourth toe and the least voltage required to elicit this movement was high (intercoil distance = 20 cm.). The wound was then closed and the animal kept until biopsy at 180 days. At this stage stimulation of the peroneal nerve elicited spreading of all three toes, together with dorsal flexion and pronation of the foot, at voltages much lower than that required to elicit the minimal spreading of the first exploration (coil distance=38 cm.).

TABLE II.—RECOVERY OF FUNCTION FOLLOWING THE UNAIDED UNION OF THE STUMPS IN THE TIBIAL NERVE. SUMMARY OF DATA.

		Motor recovery	*Recovery electrical excitability*		
Animal	*Gap*	*Time of onset*	*Time*	*Contraction of M. gastrocnemius*	*Sensory recovery*
555	27 mm.	162 d.	200 d.	+	None in 200 d
538	36 mm.	None in 123 d.	123 d.	+	None in 123 d.
557	36 mm.	None in 165 d.	165 d.	+	None in 165 d.
552	33 mm.	None in 193 d.			None in 193 d.
585	34 mm.	None in 135 d.			None in 135 d.
556	37 mm.	None in 200 d.	No visible rejunction		None in 200 d.
551	39 mm.	None in 194 d.	of stumps		None in 194 d.
639	55 mm.	None in 200 d.			None in 200 d.

The series of animals in which gaps were made in the tibial nerve when taking autografts (*see* p. 375) gave further instances of unaided union. These gaps were always longer than the gaps made in the peroneal nerve, varying from 27 to 55 mm. in extent. The results of eight cases of tibial nerve gaps are shown in Table II and Text-fig. 1. Only one rabbit out of eight (animal 555) showed any recovery of reflex function, although two others (animals 538 and 557) also showed macroscopic reunion of stumps. The reflex recovery was detected by observing the return of abduction of the first toe in the spreading reflex, and of reflex plantar flexion elicited in response to holding the animal head downwards and then suddenly lowering the whole animal. These functions first appeared 162 days

after operation, but as no way of estimating the degree of tibial nerve function had been devised, it is not known to what extent improvement took place.

The animal (555) which recovered functionally in 162 days, was reopened at 200 days, 38 days after motor recovery. Stimulation of the tibial nerve elicited contractions of gastrocnemius, and, with high voltages, visible plantar flexion of the foot, although, whatever the voltage used, only parts of the gastrocnemius ever contracted.

Animal 538, which also showed reunion of stumps, was reopened 123 days after operation, and gave responses to electrical stimulation although reflex function had not returned. In this case the least voltage required to excite *M. gastrocnemius* via the nerve was very high indeed (coil distance = 17 cm.). Again only parts of the muscle ever contracted.

Feeble contraction of parts of the *M. gastrocnemius* also followed stimulation of the tibial nerve in a third animal (557), examined 165 days after operation, but whatever the voltage used, plantar flexion of the foot could not be elicited. Although reunion of stumps had occurred no recovery of reflex function took place in this animal. However, the voltage required to elicit contractions of the gastrocnemius was fairly low (coil distance = 38 cm.) compared with the above cases. Although counts have not been made it is probable that this case represents a failure to reinnervate sufficient muscle fibres to produce a return of function. Indeed, the fact that only partial contractions ever followed stimulation of these tibial nerves indicates that partial reinnervation of gastrocnemius is all that ever follows unaided union of the tibial nerve.

Sensory recovery.—In no case, either of a peroneal or a tibial nerve gap, did any recovery of skin sensibility occur which could be definitely ascribed to regeneration. Every animal with a peroneal nerve gap, however, even those in which there was no reunion of stumps, recovered sensibility to pin-prick on the anterior part of the shank as far distally as the malleolar line. This "recovery," however, was a result of the activity of fibres running in the neighbouring high tibial, femoral and sural (saphenous minor) skin areas (*see* above, p. 376).

Histology of unaided union.—The new strand of tissue connecting the stumps in cases of unaided union consists of a matrix of connective tissue, well supplied with blood-vessels, through which the new fibres, accompanied by their Schwann cells run in irregular bundles (Plate XIV, fig. 9). The bundles of fibres in the strand run generally from the central stump in the direction of the peripheral stump, but are much looped and twisted

about one another (Plate XIII, fig. 2). Many of them become deviated. Fibres are able to become myelinated in the strand, and some of them reach a considerable thickness (Plate XIII, fig. 2). However, the extent to which they reach diameters comparable with those of the fibres of the central stump is not known.

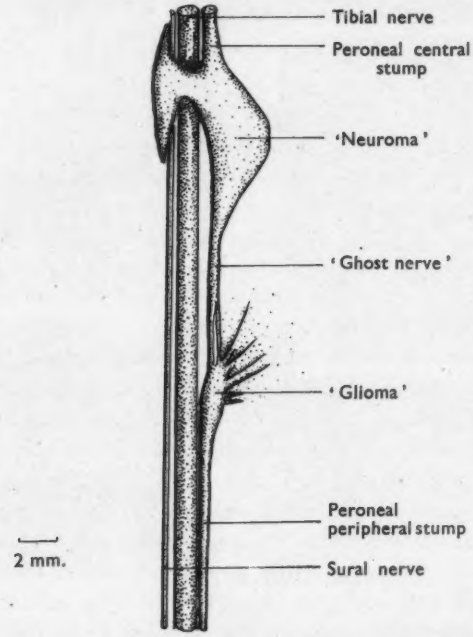
The thickness of the connecting strand relative to the thickness of the nerve, and, consequently, the number of fibres which reach the peripheral stump through it, varies in different animals. Animals 582 and 555, which recovered reflex function, had thick connecting strands arising from central stumps which were not strikingly bulbous. Animals 538 and 557, the only others with visible reunion of stumps, and which recovered electrical excitability but not reflex function, showed large central bulbs and relatively thin strands. In both cases the peripheral stumps contained relatively fewer nerve fibres than either 582 or 555. Thus there seems to be a correlation between bulb formation and the thickness of the new bridge formed between the stumps. Where a thick strand is formed the resultant bulb is small, and vice versa. This fact was noted by Guttmann and Medawar (1942), who also saw that bulbs are largest of all where no bridging strand is formed. Thus the failure to recover reflex function in those cases where electrical excitability recovered was probably due to an insufficiency of active motor units in the reinnervated muscles. The fact that only parts of the muscle ever contracted in these cases lends weight to this conclusion.

Histological comparison of the reinnervated muscles in animal 557 (which recovered electrical excitability) and animal 582 (which recovered reflex function) further supports this hypothesis. The gastrocnemius of animal 557 was but poorly innervated, some of the Schwann bands in the small nerve trunks within the muscle being empty of fibres (Plate XIII, fig. 3). The majority of the nerve fibres were thin, although there were occasional thick fibres. Only a few scattered fibres were myelinated. However, the peroneus longus in animal 582 was much more richly innervated by thick nerve fibres (Plate XIII, fig. 4). Some of the muscle endplates in this muscle were found each to be innervated by two nerve fibres (Plate XIII, fig. 5), a type of innervation which was also found after the other procedures.

These cases represent the best that can be expected after unaided unions. Fibres are able to reach the peripheral stump and reinnervate the paralysed muscles, but not in sufficient numbers to bring about a high degree of recovery. Indeed a recovery of reflex function seems to be the exception rather than the rule in unaided unions, and recovery to the stage of elec-

trical excitability without subsequent reflex recovery is probably more typical of this procedure.

The mechanism by which a new strand is formed between the stumps in cases of unaided union has been described by Nageotte (1916), Kirk and Lewis (1917), Young, Holmes and Sanders (1940). Schwann cells grow



TEXT-FIG 2.—Diagram of the sciatic nerve in the thigh in a case 200 days after the making of a gap of 2 cm. in the peroneal division. Simplified from an actual photograph.

out from the end of the peripheral stump and Schwann cells plus new fibres from the central stump. These outgrowths meet and contribute to the formation of the new strand of nerve between the stumps. Text-fig. 2 shows the way in which these processes result in the formation of a new nerve. Two hundred days after a gap of 2 cm. was made in the peroneal nerve, the central stump bore a large neuroma. The peripheral stump was swollen at its tip, and from it strands of tissue passed out into the surrounding tissue in the shape of a fan. Two arms of this fan were much more strongly developed than the others and formed the base of a

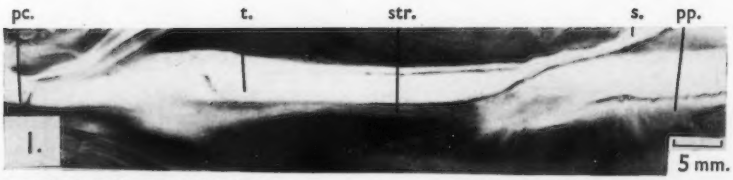
thick connecting strand or "ghost nerve" effecting a junction with the central stump. The way in which a new endoneurium is formed has been described by Masson (1932). However, little is known either of the size of the gaps which can be closed by this means, or of the factors which determine whether or not reunion shall occur. Dominici (1911) claimed to have found new fibres in the peripheral stump after the bridging of a 6 cm. gap by unaided union in a rabbit. In the present experiments the largest gap found bridged was 36 mm. Larger gaps (up to 55 mm.) showed no reunion.

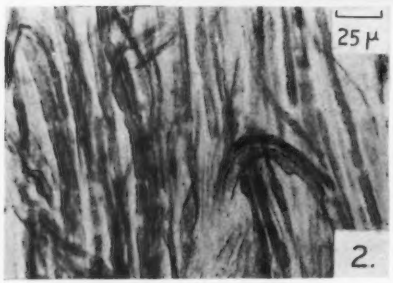
A factor which appears to favour unaided union is that of support. When there is a longitudinally directed structure next to the resected nerve, the new outgrowths tend to run along it (Plate XIII, fig. 1, also Text-fig. 2). Indeed the only cases where recovery has been reported following unaided union have been where some sort of support has been provided. Text-fig. 2 provides additional evidence of the tendency of nerve outgrowths to favour structures which give them mechanical support. A large neuroma formed from the cut central stump in this case heavily involved the tibial nerve, and, in addition to the connection between neuroma and peripheral stump, abortive outgrowths were formed on the far side of the tibial nerve, directed both up and down the nerve. Vanlair (1894) found recovery of sensation in the pads of the foot of three dogs thirteen, twenty and twenty-eight months after bridging of 1, 2, and 3 cm. gaps in the sciatic nerve.[1] In his cases support for the outgrowths was provided by alignment of the resected stumps by a pair of silk sutures connecting the epineurium of the stumps at either side of the nerve. In the present experiments support was present in the shape of unresected nerves running alongside the cut nerve. The favourable action of this factor of support may account for the occasional recoveries that have been reported, both in animals and man, following such precedures as suture à distance and tubulization (*see* Sanders, 1942).

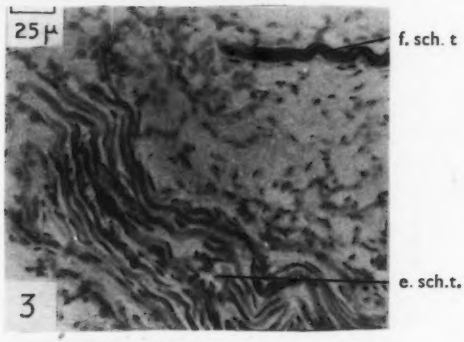
Unaided union of stumps can thus be followed by motor recovery, contrary to the opinion of Mauss (1921). This, however, is of very poor quality, and is hardly likely to occur over large gaps in man. Small gaps, however, may be closed by this means. Sharpey-Schafer (1929) cut the branch of his ulnar nerve in the radial side of the little finger, the cut

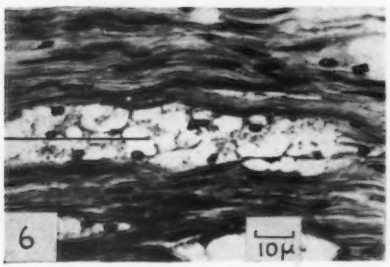
[1] These recoveries of Vanlair occurred much later than those reported here. However, it must be remembered that in the regeneration of the sciatic nerve, the muscles become reinnervated by virtue of their position long before new fibres arrive at the skin. Thus it is possible that had the animal showing motor recovery been kept as long as Vanlair's, it might have also shown sensory recovery.

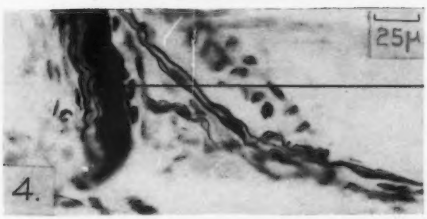
PLATE XIII.

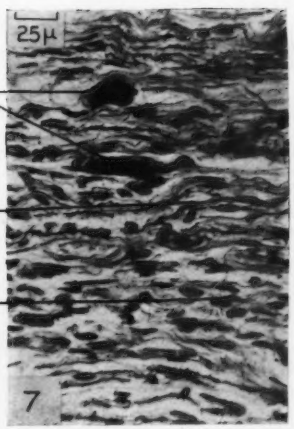






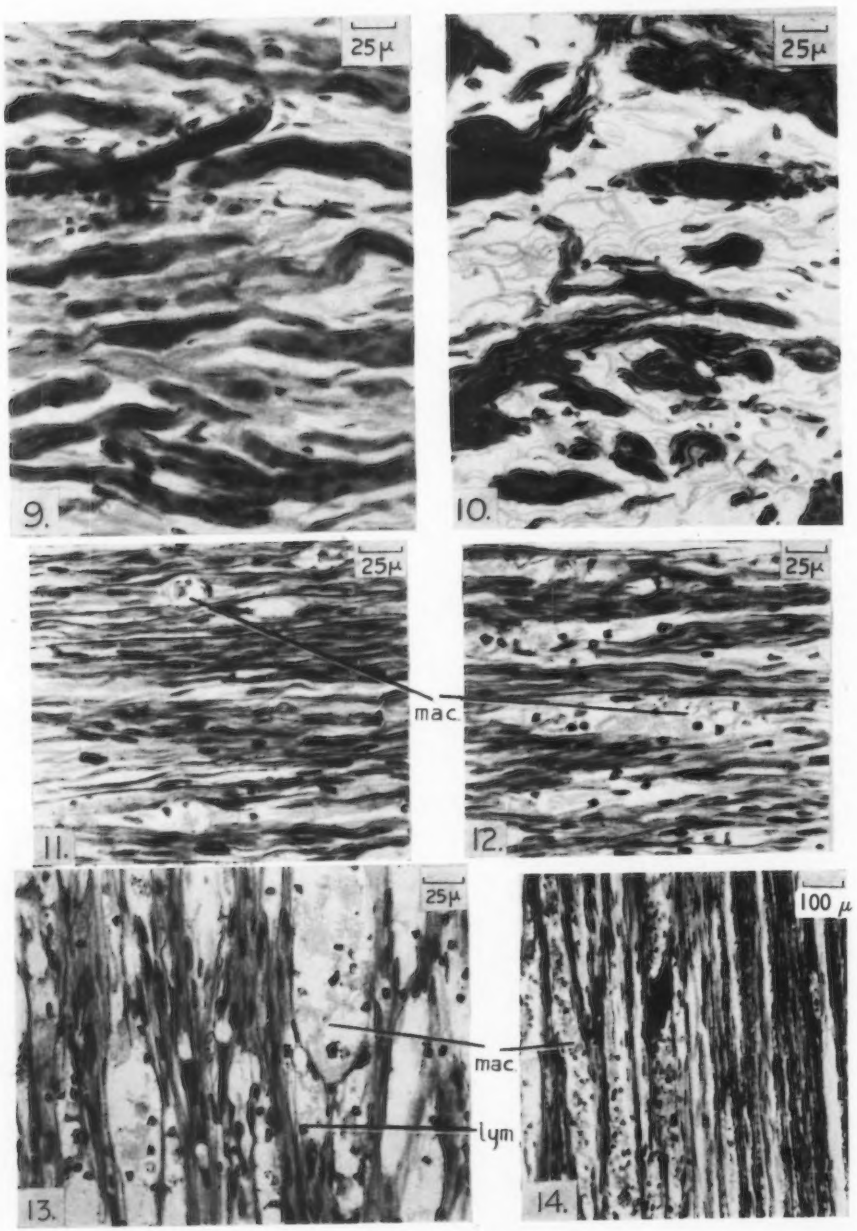






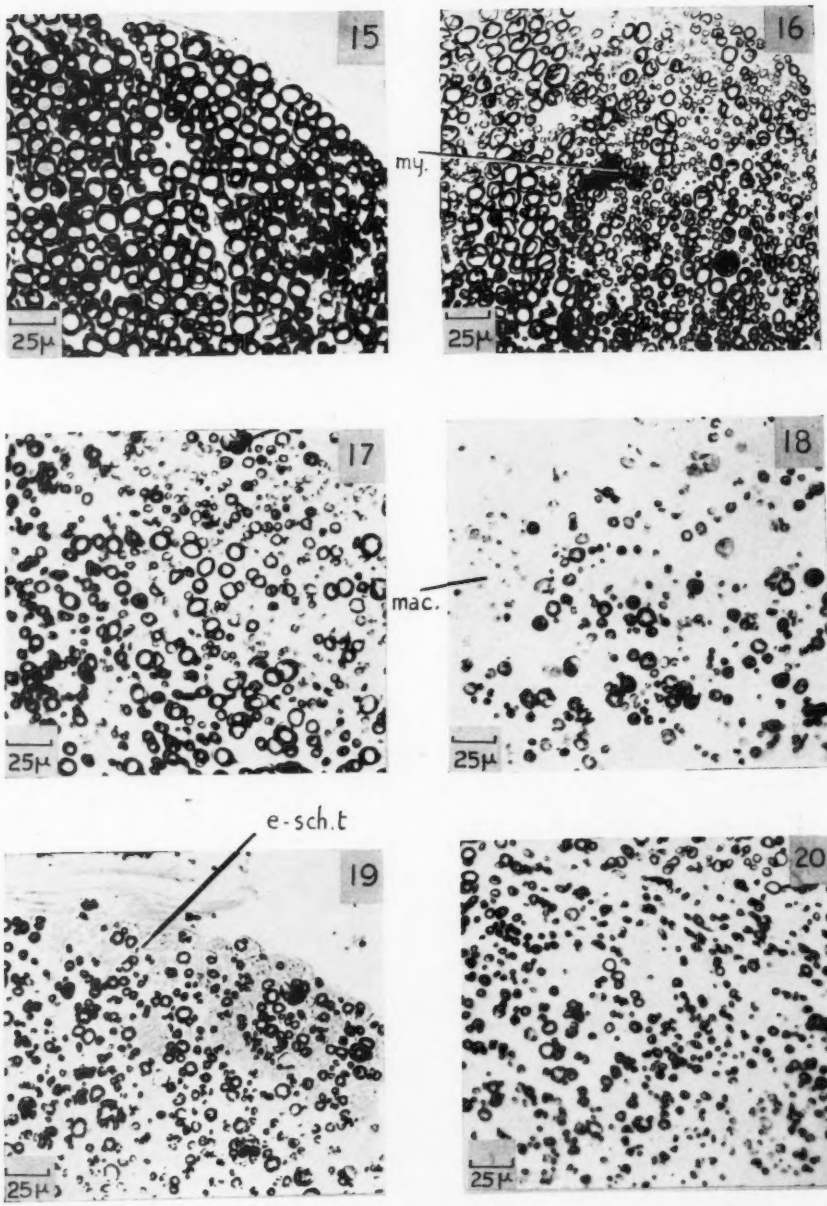
To illustrate article by E. Gutmann and F. K. Sanders.

PLATE XIV.



To illustrate article by E. Gutmann and F. K. Sanders.

PLATE XV.



To illustrate article by E. Gutmann and F. K. Sanders.

ends not being sutured together and a small gap left between them. The extent of the gap was not stated. The beginning of recovery of pain in the little finger was noted after seven months, but even after eight months this recovery was incomplete.

End-to-end Suture.

Motor recovery.—The functional results of end-to-end suture were studied in eight animals, and recovery of the spreading reflex occurred in all of them. The times at which spreading of the fourth toe (Grade 1) was first observed in these animals are shown in Table III and Text-fig. 1. It will be seen that the time of the onset of recovery varied in the different animals from fifty-six to eighty-five days.

Table III.—Recovery of Function following End-to-end Suture and Autografts. Summary of Data.

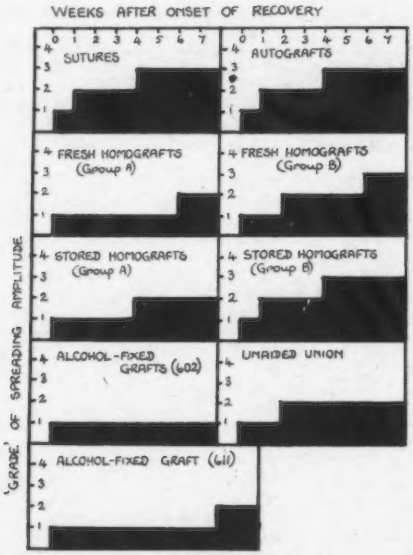
		Motor recovery						
		Time of onset	*Final grade of*	*Time of*	*Electrical excitability*			
	Animal	*days*	*spreading*	*measurement*	*d.f.*	*prn.*	*sprdn.*	*Sensory recovery*
	590	56	not noted	35 d.	+	+	+	None in 63 d.
S	671	56	3	200 d.	+	+	+	None in 200 d.
U	589	59	3	126 d.	+	+	+	Complete in 124 d.
T	669	61	3	not measured				None in 162 d.
U								
R	604	72	3	124 d.	+	+	+	Complete in 124 d.
E	521	80	not noted	94 d.	+	+	+	None in 94 d.
S	670	84	3	200 d.	+	+	+	Complete in 159 d.
	625	85	not noted	not measured				None in 114 d.
	551	51	3	194 d.	+	+	+	Complete in 174 d.
	637	52	3	not measured				None in 163 d.
A	669	59	3	not measured				None in 162 d.
U	639	68	not noted	100 d.	+	+	+	None in 100 d.
T	671	77	3	200 d.	+	+	+	None in 200 d.
O	549	80	3	182 d.	+	+	+	None in 182 d.
G	571	82	not noted	not measured				None in 102 d.
R								
A	625	98	not noted	not measured				None in 114 d.
F								
T	478	none in 102 d.		not measured				None in 102 d.
S	553	none in 135 d.		106 d.	−	−	+	None in 135 d.

d.f.=dorsal flexion, prn.=pronation, sprdn.=spreading of toes, d=days.

At the onset of recovery the amplitude of spreading was always minimal. However, its value increased progressively with time. Text-fig. 3 shows the way in which this improvement took place. One week after the onset of recovery the mean amplitude of spreading in the five

animals studied (*see* Table III) was that represented by Grade 2 in the spreading index. Two weeks later it had increased to Grade 3. No further improvement occurred, even in two animals (670, 671) kept alive for 200 days. Only five out of the eight animals which recovered the reflex survived sufficiently long to achieve a maximum grade of spreading beyond which which no further improvement took place. All five had a final grade of 3, but no animal recovered spreading of normal amplitude (Grade 4).

The eight animals were opened at different times between 63 and 200 days. In all cases the suture line was strongly vascularized, and showed as a slight bulbous enlargement in the course of the nerve. Five of these



TEXT-FIG. 3.—Diagrams to show the average improvement in the "grade" of spreading following the recovery of this reflex after end-to-end suture, various nerve grafts, and the unaided union of stumps. Ordinates: grades of spreading in the "spreading-index" (*see* text); Abscissæ: weeks following the onset of recovery.

animals were stimulated electrically, the three exceptions being animals which died before they could be brought to biopsy. In all six animals stimulation of the peroneal nerve produced contraction of all the peroneal musculature.

Sensory recovery.—Three animals out of the eight which recovered motor function (animals 589, 604, 670) made a complete sensory recovery on the dorsum of the foot. The times at which the recovery was first observed as complete were 124, 124 and 159 days after operation (*see* Table III). In the other cases no recovery took place on the dorsum of the foot. However, one of these animals (590) was brought to biopsy at a very early date (63 days), and in view of the time at which the first complete sensory recovery in the autonomous zone occurred (124 days), cannot be regarded as a failure. Two further animals (625, 521) which showed no recovery at 94 and 114 days must also be excluded. The remaining two (669, 671) showed no sign of sensory recovery when they were killed at 162 and 200 days. Since one sensory recovery took place as late as 159 days, the first of these must be a doubtful case. However, as the line of analgesia failed to begin to retreat down the dorsum of the foot in either case, they most probably represent failures.

The sensory results after end-to-end suture were thus out of five cases, three complete recoveries, and two probable failures, both the "failures" (669, 671) showed considerable separation (2 to 5 mm.) of the stumps at the suture line, and failure of sensory recovery may have been due to this factor.

Histology of end-to-end sutures.—By 162 days after suture all myelin has disappeared from the peripheral stump, although even at 200 days there are still occasional spaces containing macrophages. They are, however, very infrequent. Otherwise the stump has the appearance of normal nerve. Indeed, it is only by the occurrence of these few spaces, and by the large number of Schwann nuclei, that a regenerated peripheral stump at this stage may be distinguished from the central stump in longitudinal section on superficial examination.

At 200 days the peripheral stump below a suture contains a profusion of myelinated nerve fibres (Plate XV, fig. 16). The largest of these fibres are about equal in diameter to those of the central stump, but there are many fewer large fibres than in the central stump (compare figs. 15 and 16, Plate XV). Sanders and Gutmann (1942) studied the spectrum of fibre-sizes in the peroneal nerve of the rabbit at long periods after its lesion and repair by various procedures. In all cases the fibres in the periphery were smaller than these central to the lesion, although the latter were reduced in size as compared with normal nerve. Moreover the fibre-spectrum of the

peripheral stump did not show the separate pile of large fibres which was characteristic both of normal nerves and central stumps.

End-to-end suture thus gives a much better recovery than unaided union of stumps, both as regards time of onset and final degree, but the function never returns with the normal amplitude. Histological examination of the muscles reinnervated through a suture showed that the nerve trunks within the muscle contained a profusion of fibres, including bundles of large myelinated fibres. Thus the reinnervated muscles after end-to-end suture contain (*a*) more fibres, and (*b*) more large myelinated fibres, than the same muscles after unaided union (*see* p. 380).

Autografts.

Motor recovery.—Out of ten autografts, eight showed motor recovery, the spreading reflex appearing 51 to 98 days after the operation. The results are shown in Table III and text-fig. 1. Apart from a single late recovery (625), which was subsequently found to show a moderate amount of retraction at the lower junction, the other values show the same sort of scatter as after end-to-end sutures (51-82 days as compared with 56-85 days; *see* Table III).

On first appearing the spreading reflex was minimal (Grade 1). Thereafter it increased in amount. Five animals (*see* Table III) were followed for sufficiently long to achieve a maximal degree of spreading. The way in which this occurred is shown in text-fig. 3. One week after the onset of recovery, the degree of spreading had progressed from Grade 1 to Grade 2 of the spreading index. After a further two weeks it had reached Grade 3. No further improvement occurred although three animals (549, 551, 671) were kept alive for 182, 194, and 200 days, 81, 123, and 102 days after the respective animals had attained the maximum degree of spreading. All the five animals recovered as far as a spreading-index of Grade 3, exactly as in end-to-end sutures. From a comparison of the diagrams for autografts and end-to-end sutures in text-fig. 3, it will be seen that, following the onset of recovery the rate of improvement in the grade of spreading was identical in the two cases.

At sacrifice, the graft appeared well united with its host nerve in all the above cases. It was white, healthy, well vascularized by vessels running along the nerve, and looked exactly like normal nerve. There was

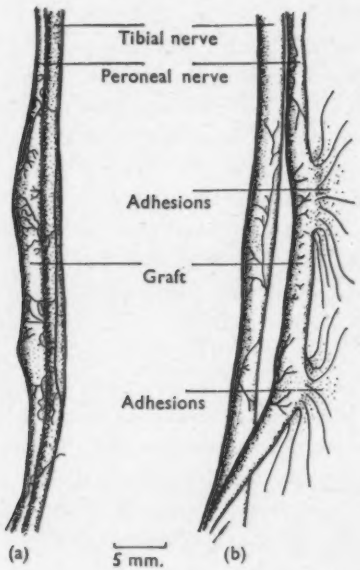
no sign of the capsulation or fibrosis which occurred in some other types of graft.

The results of stimulating the peroneal nerve in six of these autografts, opened at 64, 100, 106, 182, 194 and 200 days respectively, were as follows: in all except one animal (553, *see* Table III) fairly low voltages of stimulation produced dorsal flexion and pronation of the foot, and spreading of the second, third and fourth toes, indicating reinnervation of all the peroneal musculature. In the excepted case, an animal which had shown no recovery of reflex function and was opened at 106 days, the only reaction which could be elicited electrically was weak spreading of the fourth toe, indicating reinnervation of the abductor digiti quarti, which is one of the most proximally situated of the muscles involved in the spreading reflex. The wound was accordingly closed and the animal returned to its cage. Subsequently it died at 133 days without recovering reflex spreading.

A further animal (520), not included in the data of Table III, was opened at 64 days—before recovery of the spreading reflex had occurred —and stimulated electrically. High voltages (coil distance = 17) elicited dorsal flexion and pronation of the foot, and spreading of the toes. Therefore reinnervation of all the peroneal musculature had taken place although it was not yet functioning, presumably owing to incomplete " maturation " in the trunk (*see* Sanders and Gutmann, 1942). Recovery of electrical excitability always precedes recovery of reflex-function, and it has been shown (*see* p. 380) that it can occur without subsequent reflex recovery.

Sensory recovery.—Four animals were followed for more than 124 days —the time (*see* Table III) at which the earliest sensory recovery occurred after end-to-end suture. One of these made a complete sensory recovery in 174 days. The other three, one case at 162 days (669), one at 182 days (549), and one at 200 days (671) showed no recovery of sensation within the autonomous zone of the peroneal nerve. Autografts thus showed one sensory recovery in four, as compared with three out of five after end-to-end suture. However, the time of incidence of sensory recovery in the autograft was late compared with those of sutures, and it is possible that the so-called " failures " were not followed long enough really to merit inclusion in that class. One hundred and seventy-four days may well represent a precocious recovery of sensation after autografts, and recovery may occur later than 200 days, the time at which the latest animal was killed. However, sensory recovery after autografting does seem to be distinctly less good than after suturing.

Histology of autografts.—At biopsy 200 days after operation autografts looked like slightly thickened segments of normal nerve. The junctions were not markedly bulbous, there were no extensive adhesions, and the



TEXT-FIG. 4.—Tracings from photographs, taken 200 days after operation, of (*a*) an autograft (animal 671) and (*b*) a fresh homograft (animal 658). Note adhesions in the homograft. Sural nerve not shown..

grafts were well supplied with blood-vessels (*see* text-fig. 4). Sanders and Young (1942) have shown that degeneration and reinnervation proceeds very similarly in an autograft and a normal peripheral stump. However, the processes take a little longer in an autograft. In the present series, at 64 days an autograft may still be distinguished from a normal peripheral stump by the fact that the graft contains slightly larger spaces containing myelin debris and macrophages (cf. Plate XIV, figs. 11 and 12). However, even as late as 100 days an autograft still contains macrophages filled with degenerated myelin as well as new myelinated fibres. However, at 162 days all myelin remains have disappeared, and at 200 days an autograft

is no longer distinguishable from a normal peripheral stump, both containing occasional macrophages.

Myelination proceeds almost as rapidly and completely in a rabbit tibial autograft as in a normal peripheral stump. At 200 days there are many fibres of a range of sizes but the largest fibres are slightly smaller and more infrequent than those of the central stump (Plate XV, fig. 17). Sanders and Gutmann (1942) have shown that in autografts at 200 days, as well as in normal peripheral stumps, there is no pile of large fibres in the fibre-size histogram, such as occurs in normal nerve.

Autografts of this size show no patches of necrosis in the centre of the graft, and there are no patches in the graft, which contain either none or only small fibres, as seems to occur in fresh homografts (*see below*, p. 395). At 200 days there is no sign of the lymphocyte aggregates or blood-vessel dilatation occasionally seen in the early stages after autografting in the rabbit (*see* Sanders and Young, 1942, Plate XIII, figs. 6 and 7).

At 200 days the junctions in those autografts which showed motor recovery were indistinguishable from those of sutures. Indeed, they were usually more closely made, some slight retraction occurring occasionally in sutures, but never in autografts.[1] There was occasional fibrosis, but this was not restricted to the lower junction (*see* Davis and Cleveland, 1934). Indeed the lower junctions generally showed less criss-crossing and obstruction of fibres, more fibres running straight through. These results confirm the conclusions of Sanders and Young (1942), from a study of early stages, that under the best conditions perfectly smooth primary junctions could be made, both proximally and distally, and that there was no experimental foundation for the practice, suggested by some authors (Lewis, 1923, Davis and Cleveland, 1934) of severance and resuture of the lower junctions of grafts to prevent excessive fibrosis from obstructing the outgrowth of fibres.

However, three extra cases of autografts were found in which the lower junctions had become detached. They showed no motor recovery, and since its failure was obviously due to the detachment of the lower junction, and not to any intrinsic inability of the graft to act as a conduit for new nerve fibres they were not included in the statistics of Table III. In all

[1] However, in three cases in which motor recovery failed to appear, complete separation of the lower junction was found to have taken place (*see below*).

three cases, opened respectively at 83, 141, and 200 days,[1] the lower end of the graft was found separated from the peripheral stump, but there was always a thin thread of tissue visible connecting the stumps, exactly similar to the connecting strand of an unaided union.

No case was found in which the proximal junction became detached. Thus detachment of the lower junction is a factor which may cause failure of recovery in autografts placed in the peroneal nerve in the rabbit and sutured with plasma, and it is probable that resection of the connecting strand and resuture of the graft and peripheral stump might have been successful in promoting recovery in these cases. However, it is undoubtedly a purely mechanical phenomenon. Considerable tension is exerted upon the peroneal nerve by extension of the leg, as exemplified by the difficulty experienced in getting the stumps together when making a suture of this nerve with the rabbit's leg in extension. Moreover, when a plasma junction is made, the plasma, besides fixing the stumps together, may also stick the nerve to the underlying fascia. Thus, if the rabbit extends its leg in the period immediately following the placing of the graft, tension will be exerted directly upon the lower junction, and if this has not been firmly made, it may give way. In spite of all this there is no doubt that perfectly firm primary lower junctions can be made with plasma.

The two cases in Table III in which failure of recovery was not referable to detached junctions (animals 478 and 553) gave specimens in which the graft was found to be very thin, full of patches of macrophages and containing fewer and thinner fibres than the 64 days' stage. The peripheral stumps were very poorly innervated, and, in animal 553 the peripheral stump was found to contain very few nerve fibres. Both were old animals, however, and in very poor health throughout the experiment, and delay of degeneration and failure of regeneration may have been due to this cause.

In three cases autografts were compared directly with end-to-end sutures in the same animal (rabbits 625, 669 and 671). From Table III it

[1] In most of the animals described in this paper the progress of atrophy in the paralysed muscles was followed by successive measurements of the circumference of the leg in the way described by Gutmann (1942). After operation circumference steadily declined until just before motor recovery, when it began to increase. The beginning of a steady increase in leg circumference was thus a sign of approaching motor recovery. In these three animals no such increase was seen, only a steady decrease, and on this evidence the re-explorations were made.

will be seen that in two cases the suture recovered first, and in the third the autograft. It will be noted that when the sutures recovered first, thirteen and twenty-one days elapsed before recovery of the autograft, whereas in the third case the graft recovered only two days earlier than the suture on the opposite side. This indicates that perhaps sutures may recover a little earlier than autografts, owing to the greater latent period and slower rate of fibre growth in autografts (*see* Sanders and Young, 1942) but that the small difference which this factor produces is in practice obscured by the normal variation due to individual differences in the rate of regeneration.

Comparison of the reinnervation of the peroneus longus 200 days after sutures and autografts reveals no difference in either thickness or myelination of nerve fibres. Thus a 2 cm. autograft of the thickness of the rabbit's tibial nerve is able to produce a reinnervation indistinguishable from that following simple primary end-to-end suture of the cut nerve.

Functional recovery following autografting in animals has been reported by a number of authors. A review of these investigations is given by Sanders (1942). Apart from the experiments of Bentley and Hill (1936), previous investigators have dated the appearance of the signs of voluntary movement much later than has been recorded in the present experiments. However, the majority of reports are based upon observations of the return of either (*a*) electrical excitability or (*b*) normal gait, both of which are neither reliable nor exact tests of functional recovery (*see* Gutmann, 1942).

Homografts.

Motor recovery.—Ten fresh homografts were made. One animal was killed 61 days after operation—before motor recovery was likely to have occurred. Two of the others developed sores of the dorsum of the foot on the operated side which made it impossible to observe the spreading reflex. These three cases were discarded from the series. Out of the remaining seven animals, six recovered spreading. The times of onset of the reflex in these animals were scattered between 70 and 125 days, and are given in Table IV and text-fig. 1. These data indicate that fresh homografts recover a little later than autografts or end-to-end sutures, but the difference is hardly enough to be significant.

TABLE IV.—RECOVERY OF FUNCTION FOLLOWING FRESH HOMOGRAFTS. HOMOGRAFTS STORED IN RINGER'S SOLUTION AT 2° C., AND ALCOHOL-FIXED GRAFTS. SUMMARY OF DATA.

			Motor recovery (sprdn.)		*Electrical excitability*				
		Animal	*Time of onset*	*Final grade of sprdn.*	*Time*	*d.f.*	*prn.*	*sprdn.*	*Sensory recovery*
	H								
	O	555	70 d.	3	200 d.	+	+	+	Complete in 185 d.
	M	557	72 d.	3	165 d.	+	+	+	Incomplete 165 d.
F	O	556	84 d.	2	200 d.	+	+	+	Incomplete 200 d.
R	G	658	84 d.	2	200 d.	+	+	+	Complete in 172 d.
E	R	638	85 d.	not noted	100 d.	+	+	+	None in 100 d.
S	A	657	125 d.	2	200 d.	+	−	+	None in 200 d.
H	F	585	None in 135 d.	0	135 d.	−	−	−	None in 135 d.
	T								
	S								
	H								
	O	613	61 d.	3	124 d.	+	+	+	None in 124 d.
S	M	602	70 d.	2	200 d.	+	+	+	Incomplete 200 d.
T	O	647	71 d.	3	200 d.	+	+	+	Complete in 174 d.
O	G	658	75 d.	3	200 d.	+	+	+	Incomplete 200 d.
R	R	611	82 d.	2	200 d.	+	+	+	None in 200 d.
E	A	612	84 d.	3	200 d.	+	+	+	None in 200 d.
D	F	601	86 d.	not noted	not measured				None in 117 d.
	T								
	S	657	117 d.	3	200 d.	+	+	+	None in 200 d.
	G	611	126 d.	2	200 d.	+	+	+	None in 200 d.
F	R	602	142 d.	1	200 d.	+	+	+	None in 200 d.
I	A	601	None in 117 d.	0	not measured				None in 117 d.
X	F								
E	T	612	None in 200 d.	0	200 d.	−	−	−	None in 200 d.
D	S								

d.f.=dorsal flexion, prn.= pronation, sprdn.=spreading of the toes, d.=days.

Table IV shows the final amplitude of spreading attained in the different homografts. Out of five animals followed for a sufficiently long time, three finally attained a spreading-index of Grade 2, and two an index of Grade 3. Text-fig. 3 shows the way in which the final grade was attained in both these groups of animals. In text-fig. 3 the diagram marked group (*a*) represents the mean course of recovery in those animals which recovered a final amplitude of Grade 2, group (*b*) those animals which finally attained Grade 3. Following the onset of recovery at Grade 1, spreading of Grade 2 did not appear until two weeks later in group (*b*), and six weeks after the onset of recovery in group (*a*). Thereafter no further improvement occurred in the animals of group (*a*) (556, 657, 658), although all three animals were kept alive for 200 days following operation. Grade 3 spreading was attained six weeks after the onset of recovery in group (*b*) animals (555, 557), and thereafter the spreading-index continued unchanged at this grade. The increase in spreading amplitude following the onset of recovery was thus quicker in group (*b*) than in group (*a*) and a larger final

amplitude was attained. Moreover, group (*b*) animals showed an earlier onset of motor recovery than group (*a*) (70 and 72 days as compared with 84 days and 125 days; *see* Table IV), thus confirming the conclusion of Gutmann (1942) that the earlier the onset of recovery of spreading, the greater the final amplitude attained.

This division of homografts into two groups, both as regards the time of onset of recovery and the final amplitude of spreading attained, although it was made arbitrarily, is strongly suggestive of the bimodal distribution seen by Sanders and Young (1942) in the distances reached at 25 days by pain fibres growing through fresh homografts.

Although, in favourable cases, homografts are able to attain the same final amplitude of spreading as autografts or end-to-end sutures, the majority of cases show a distinctly smaller amplitude of spreading (Grade 2 as compared with Grade 3), and even in the best cases a longer time elapses between the onset of recovery and the attainment of the final grade than in autografts or sutures (*see* text-fig. 3).

After 135 to 200 days in the host homografts, like autografts, had the macroscopic appearance of normal nerve. They were white, vascularized, and looked like slightly thicker segments of the host nerve. However, they showed a certain amount of fibrous adhesion between the graft and its bed (*see* text-fig. 4 (*b*)). In one animal (585) in which recovery failed, the whole bed of the nerve was filled with connective tissue and masses of fat, the graft itself being pale and transparent, and of much smaller diameter than the host nerve.

Stimulation of the peroneal nerve at the time of biopsy in six cases elicited dorsal flexion, pronation, and spreading of the toes, indicating that new fibres had reached and reinnervated all the muscles supplied by the peroneal nerve. Three further cases gave different results. One (animal 585) showed a complete absence of indirect excitability at 135 days, even with very high voltages of stimulation (coil distance = 12 cm.). The second (538) failed to show spreading in response to stimulation, although dorsal flexion and pronation were elicited, but as this was one of the animals in which a sore had developed, this result cannot be taken as definitely indicating an absence of reinnervation of the small peronei I-IV. The third case (657), an animal opened at 200 days which had made a late (125 days) recovery of spreading, gave only weak spreading and dorsal flexion in response to stimulation, with an absence of pronation.

Sensory recovery.—Seven animals were followed for more than 124 days, and two recovered sensation completely on the dorsum of the foot in 172 and 185 days respectively. In two animals recovery failed to progress below the malleolar line, although they were kept alive for 200 days. In a third (135 days) sensory recovery failed entirely, in addition to motor recovery and indirect excitability (animal 585). The two remaining cases made incomplete recoveries. One showed a retreat of the line of analgesia as far as the middle of the foot when brought to biopsy at 200 days. In the last, recovery was still incomplete at 165 days. This animal was of interest as the advance of recovery on the dorsum of the foot was anomalous. Three to four weeks after operation the animal developed a sore on the lateral aspect of the distal half of the dorsum of the foot. Pricking the foot 17 mm. from the malleolar line twenty-one days after operation induced positive responses. This region thus contained nerve fibres, presumably coming in with the new blood-vessels running to the walls of the sore, since it was too early for regeneration to have occurred. Two months after operation the sore began to heal, and the line of analgesia advanced with the border of the healing sore, so that sixty-three days after operation there was clear progress of the analgesic line 28 mm. below the malleolar line. Progress continued to 34 mm. below the malleolar line, when the line of analgesia ran diagonally across the dorsum of the foot, the least progress being laterally, while on the medial side the line was only 12 mm. from the base of the first phalanx. This state remained until 165 days, when the animal was killed. At this time the skin in the region of the healed sore was dry, flaky, and showed clear "trophic" changes. Whether the advance of the line of analgesia in this case was due to regeneration or to excessive local extension of the nerve fibres in the skin (*see* Weddell *et al.*, 1942) as a result of disturbances of the pattern of skin innervation resulting from the sore, it is impossible to be certain. This case is therefore best excluded on these grounds.

Thus, out of six homografts, two recovered completely, one incompletely, and three failed. However, in view of the incomplete recovery, and the late date of the two complete recoveries, absence of recovery at 200 days does not exclude the possibility of still later recovery. Homografts therefore give a sensory recovery approximating to that of autografts, but distinctly less good than that following a suture.

Histology of fresh homografts.—Degeneration in fresh homografts takes place more slowly than in autografts, so that unbroken myelin

segments are found in such a graft at 25 days (*see* Sanders and Young, 1942). The results of this late breakdown of myelin are seen in the later stages. A homograft of 61 days contained large spaces full of active macrophages (Plate XIV, fig. 13), and grafts as late as 200 days may still contain similar, though smaller, macrophage-filled spaces (Plate XIII, fig. 6), although, in other cases, they may contain no more such spaces than does an autograft (Plate XIII, fig. 7).

The sixty-one day homograft also contained many lymphocytes (Plate XIV, fig. 13), a relic of the intense lymphocyte reaction often present in the early stages (Sanders and Young, 1942). Lymphocytes are rarely found in the later stages (Plate XIII, figs. 6 and 7).

The result of these reactions is to give a graft in which there may be patches of fibrosis (Plate XIII, fig. 7), and to cause disturbances of the pattern of the graft. Nevertheless, many fibres are able to penetrate such a graft, although, owing presumably to the obstruction of the outgrowth of Schwann cells and fibres by the patches of macrophages and lymphocytes within the graft, a graft at sixty-one days showed fewer, thinner, and more deviated fibres than an autograft of corresponding age (cf. Plate XIV, fig. 13 with figs. 11 and 12). Moreover, a less uniform innervation of the graft results. Although new fibres are able to penetrate the whole graft and to become myelinated in it, the large fibres are irregularly distributed and there are parts of the graft containing either none or only small fibres (Plate XV, fig. 18), and there are generally fewer fibres at the centre of the graft. Gutmann and Sanders (1942) have found that the largest myelinated fibres in a homograft 200 days after insertion are smaller than in an autograft, and there is no separate large fibre group in the fibre-distribution histogram.

Homografts can make very close junctions with the host nerve, but there is often considerable fibrosis. However, the reaction is equally intense at both junctions.

The case in which there was no recovery of either electrical excitability or reflex function (animal 585) had a graft which was very thin and surrounded by connective tissue. It contained very few nerve fibres and was extensively collagenized. The peroneus longus supplied by this nerve also contained very few thin fibres. By contrast, the peroneus longus innervated through the successful homografts was indistinguishable from that supplied through an autograft or an end-to-end suture.

Fresh homografts are thus capable of conducting a sufficient number of fibres to the periphery, and these fibres are able to become sufficiently

myelinated, to enable a recovery of reflex motor function to take place. The functional results, however, are distinctly inferior to those of autografts, and this is undoubtedly due to the occurrence of undesirable cell reactions in the early stages after the insertion of homografts.

There are several reports of functional recovery following fresh homografts in animals. They are either reports of a return of electrical excitability or of improved gait, and have been reviewed by Sanders (1942).

Homografts Stored in Ringer's Solution at 2° C.

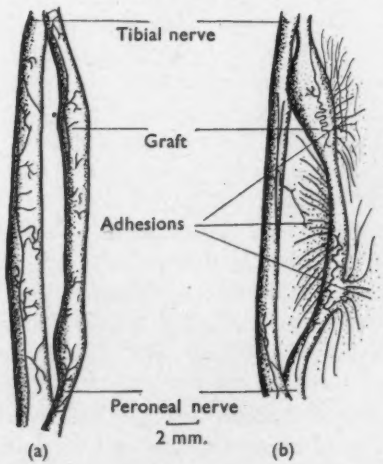
Motor recovery.—Stored homografts were inserted in the peroneal nerves of eight rabbits, five being stored for seven days prior to insertion, two for fourteen days, and one for twenty-one days. All eight animals recovered spreading between 61 and 117 days after the operation. There seemed to be no correlation between the time of storage of the graft and the time of onset of recovery. The latest recovery (117 days; *see* Table IV) was recorded in an animal with a graft stored for 14 days, but the other 14-day graft recovered 75 days after operation, and the graft stored for 21 days at 71 days. However, the animal with this late recovery (117 days, 657) lost a great deal of weight directly after the operation, and was in a more or less unhealthy state throughout observation. On the opposite side to the 14-day stored graft it bore a fresh homograft in which recovery was also delayed (*see* Table IV), and the late onset of recovery may thus have been due to the bad health of the animal rather than bad reaction to the graft. Histologically, the graft in this animal showed no abnormalities. Recovery in the other cases of stored homografts began at times of the same order as those recorded for fresh homografts—i.e. rather later than autografts or end-to-end sutures. Text-fig. 1 shows that recovery in stored homografts takes place a little earlier than in fresh grafts.

The maximal grades of spreading attained by stored homografts are shown in Table IV. Out of seven animals five recovered a spreading-index of Grade 3, while two recovered as far as Grade 2 only. The final grade of spreading obtained after stored homografts was definitely superior to that obtained after fresh homografts, although slightly inferior to the results of autografts and sutures. There was no correlation between time of storage and the final grade of spreading attained.

Text-fig. 3 shows the mean course of recovery in the two sets of stored homografts—those which had a final spreading-index of Grade 2 (animals 602, 611), group (*a*); and those which finally attained Grade 3 spreading (animals 613, 647, 658, 612, 657), group (*b*). In the animals of group (*b*)

spreading of Grade 2 amplitude first appeared one week after the onset of recovery, and increased to Grade 3 after another three weeks, a recovery more rapid than in fresh homografts (see text-fig. 3) and the same as that obtained after autografts or end-to-end sutures. No further improvement beyond Grade 3 took place, although four animals of this group were kept alive for 200 days. Group (*a*) animals took on the average four weeks after the onset of motor recovery to attain Grade 2 of spreading amplitude, and thereafter no improvement took place although both animals were kept alive for 200 days.

Thus, like homografts, stored homografts may be divided into two groups, one of which shows a more rapid and complete progression of motor recovery than the other. However, in the case of stored homografts the grafts that showed the earliest signs of the onset of motor recovery did not recover a higher grade of spreading than later animals. Animal 602, which made the second earliest recovery (70 days: *see* Table IV) only recovered a final spreading amplitude of Grade 2, while animal 657, which did not begin to recover until 117 days after operation, recovered as far as Grade 3. In spite of the appearance of this bimodality, stored homografts gave a distinctly better recovery than fresh homografts, most of the animals recovering spreading of greater amplitude.



TEXT-FIG. 5.—Tracings of photographs, taken 200 days after operation, of (*a*) a stored homograft (animal 602) and (*b*) an alcohol-fixed graft (animal 611). Note extensive adhesions and central bulb in the alcohol-fixed graft. Sural nerve not shown.

At biopsy all the grafts except two resembled normal nerve (text-fig. 5 (a)). There were none of the fibrous adhesions characteristic of fresh homografts. One of the two exceptions (611) was enclosed in a mass of proliferated connective tissue, and the other (601) had a yellowish shrunken appearance, although it was well vascularized. However, both of these showed recovery of reflex function, one at 82 days and the other at 86 days (*see* Table IV).

Seven of these stored homografts were tested for electrical excitability, one animal at 124 days (613) and the other six at 200 days after operation. In all seven animals stimulation elicited dorsal flexion, pronation, and spreading of the toes, indicating reinnervation of all the peroneal muscles.

Sensory recovery.—Excluding the two animals in Table IV which were re-opened at 117 and 124 days, almost certainly before sensory recovery could have occurred, six animals were followed for 200 days. One recovered completely in 174 days, and two others had recovered as far as the middle of the dorsum of the foot in 200 days. The rest showed no progression of the analgesic line beyond the malleolar line in 200 days. Thus, at 200 days, 1 stored homograft (stored 21 days: 647) had completely recovered sensation, while in two it was incomplete. Almost certainly 200 days is too early a date to exclude the possibility of later recoveries.

Histology of stored homografts.—After all three periods of storage and 200 days in the host there were very few, if any, spaces in the graft filled with macrophages and tissue debris (Plate XIII, fig. 8). There was no sign of the excessive macrophage reaction which was found to be a feature of the early stages of the reinnervation of these grafts (Sanders and Young, 1942). In a graft examined at 73 days, however, there were a number of macrophage-filled spaces—more numerous towards the edges of the graft (Plate XIV, fig. 14), although as early as 124 days these spaces had become smaller and fewer. At 200 days, however, there were often aggregations of macrophages and fibroblasts in the junctions, usually towards one side of the junction, and occasional patches of fibrosis within the graft. There was no trace of a lymphocyte infiltration, and the grafts were well supplied by large dilated blood-vessels. Many Schwann cells were found in these grafts, and many new fibres were present (Plate XIII, fig. 8).

Nerve fibres are able to become myelinated within these grafts, so that at 200 days a considerable range of fibre sizes is present (Plate XV, fig. 19). Sanders and Gutmann (1942) have found that stored grafts, like all other types of nerve graft, have a fibre distribution histogram which shows no large fibre pile, but that the large fibres in the graft, while still smaller

than those in the central stump, or yet in a peripheral stump below a suture, are more numerous than those in a fresh homograft or alcohol-fixed graft.

Under favourable conditions stored homografts may make as close junctions with the host nerve as fresh autografts, and many fibres are able to enter these grafts.However, fibrosis at either upper or lower junction can occur although the junctions made by stored homografts definitely allow the passage of more fibres than the junctions of fresh homografts.

In two cases fresh homografts were compared directly with stored homografts in the same animal (657, 658). In one case recovery was late on both sides, but, nevertheless, the stored homograft was the first to recover in both cases, and in both cases a higher grade of spreading was finally achieved on the stored side. Histologically, reinnervation of the peroneus longus showed no differences between the two sides.

Thus it is probable that storage of homografts in Ringer's solution at 2°C. is advantageous, in that it promotes a better degree of recovery. This is presumably brought about by reduction of the undesirable cell reactions, as already described by Sanders and Young (1942). However, the recovery following stored homografts is perhaps slightly inferior to that following autografts or sutures, and this is probably due to the excessive numbers of macrophages which enter the graft in the early stages. It is possible, however, that means will be found to overcome these disadvantages.

Functional recovery following the use of nerve grafts stored in Ringer's solution has not previously been reported. The results of other methods of nerve storage have been discussed by Sanders (1942).

Dead Grafts of Alcohol-fixed Nerve.

Motor recovery.—Four of these grafts were made, and their functional results are shown in Table IV and text-fig. 1. Only two recovered spreading, at 126 and 142 days respectively. These times of onset are much later than those recorded for the other types of graft, and are comparable to those obtained after the unaided union of stumps (*see* text-fig. 1). Such late recoveries are to be expected if these grafts act as " replacement " grafts, the new outgrowths advancing slowly as the graft is removed.

The progress of recovery in these two cases is shown in text-fig. 3. In one animal the amplitude of the spreading reflex never progressed beyond Grade 1, while in the other it increased to Grade 2, eight weeks after the onset of recovery. Thereafter neither animal made any further progress.

although both were kept alive for 200 days. These degrees of spreading are of the order obtained after the unaided union of stumps, and less than those generally obtained after other types of grafts.

One of the unrecovered grafts was exposed at 117 days, following the death of the animal. There was no sign of the graft tissue, the central stump showing a considerable neuroma, adherent to the medial surface of m. biceps femoris, and the peripheral stump a fan-shaped proliferation, adherent to the fascial bed of the nerve. There was no sign of junction, and there was a gap between the stumps of 37 mm. The other three animals, all opened at 200 days, showed a thick white strand of tissue connecting the stumps, and the central stump was bulbous (text-fig. 5 (b)). There were also adhesions between the " graft " and its bed. These were more extensive than in any other kind of graft. One of these cases showing junction failed to recover spreading (612). In this case electrical stimulation of the nerve in the thigh, even with high voltages (coil distance = 12 cm.), failed to elicit any contraction. The other two grafts responded to electrical stimulation, one by dorsal flexion, pronation and spreading, and the other by dorsal flexion and weak spreading without pronation. Both of these grafts were controlled against stored homografts and in both cases the stored homograft made an earlier and more complete recovery.

Sensory recovery.—None of these grafts showed any recovery on the dorsum of the foot in 200 days. In all cases the line of analgesia advanced as far as the malleolar line, but thereafter made no further progress.

Histology of alcohol-fixed grafts.—The details of the early stages of the replacement of these grafts by the host tissues have been described by Sanders and Young (1942). By 200 days the process is complete. The " graft " consists of a number of irregular bundles of nerve fibres, with their Schwann cells, running in a mass of connective tissue joining the two stumps (Plate XIV, fig. 10). The structure of this region is remarkably similar to the strand connecting the stumps after unaided union (cf. Plate XIV, fig. 9 with fig. 10). Although much criss-crossing of fibres takes place in the region of the junctions, the bundles run roughly parallel in the region of the "graft," so that the transverse section has the appearance of parallel columns surrounded by an " epineurium," which was interpreted by Nageotte (1917) as the reinnervated original tissues of the graft. However many fibres undergo deviation, especially at the junctions, and many fewer fibres reach the peripheral stump than originally left the central stump.

By 200 days fibres have become myelinated in the "graft" (Plate XV, fig. 20) and there are a few large fibres, but the majority of them are very small. In fact Sanders and Gutmann (1942) found the average fibre-size in alcohol-fixed grafts to be smaller than in any other type of nerve graft at 200 days.

Alcohol-fixed grafts, then, produce no better recovery than the unaided union of stumps. Indeed, the means by which an alcohol fixed graft guides fibres to the peripheral stump is essentially that of the unaided union of stumps. The only possible advantage of the alcohol-fixed tissue is that it may provide, during its removal by macrophages, an efficient support for the outgrowth of tissue from the two stumps. This in fact seems to be the case (Sanders and Young, 1942).

Discussion

The results of these experiments show that recovery of reflex motor function can follow all the types of nerve junction tested, namely end-to-end suture, autografts, fresh homografts, homografts stored in Ringer's solution at 2°C., dead alcohol-fixed grafts, and unaided unions. *Incorporated grafts*, that is grafts whose tissues survive and are incorporated into those of the host nerve, show an earlier recovery than *replacement grafts*, which are replaced by the tissues of the host, or unaided unions, 51 to 125 days as against 117 to 162 days. However, between the various types of incorporated graft there are no striking differences in time of onset of recovery. Such differences as there are correspond to predictions based on the different histological conditions shown by the various grafts in the early stages following their insertion (*see* Sanders and Young, 1942). Autografts, in which the degeneration is delayed but not strikingly abnormal, and through which new fibres grow only slightly more slowly than through a normal peripheral stump, without any great delay at the extra point of junction, recover at approximately the same time as end-to-end sutures. Lymphocyte infiltrations and patches of necrosis often occur in the early stages of fresh homografts, in addition to greatly delayed and abnormal degeneration and a slow rate of penetration by fibres. Thus homografts recover a little later, although not so much later as might be expected from their histology. Storage of homographs, which in the early stages reduces the lymphocyte reaction, appears to be followed by a recovery intermediate in time of onset between that given by autografts and fresh homografts, although the actual differences recorded can hardly be significant. Perhaps a factor militating against the still earlier recovery of stored homografts is

the excessive invasion of such grafts by macrophages in the early stages. Alcohol-fixed grafts, in which the outgrowths from the cut stumps advance slowly with the mass of macrophages removing the grafts, recover very late.

The degrees of functional recovery attained after the different types of graft show more striking differences. First, true normality of function was never attained after any procedure, even end-to-end suture. Secondly, differences in the degree of recovery of function seen after different types of graft correspond more closely to the histological abnormalities of degeneration and reinnervation of the various grafts than do the times of onset of recovery mentioned above. Indeed, all the evidence points to the conclusion that the main influence of the different histological conditions seen in the early stages of incorporated grafts is upon *degree* rather than time of onset of recovery. Fibres are able to penetrate all incorporated grafts in fairly large numbers, and the rates of penetration in the different grafts are sufficiently varied to account by themselves for the difference in the times of onset of recovery recorded (*see* Sanders and Young, 1942). Homografts, where the tissue reactions are maximal, give a somewhat poorer degree of recovery than any other incorporated graft. Autografts, whose behaviour is very like that of a normal peripheral stump, give a recovery of the same degree as end-to-end sutures. Ringer-stored homografts, in which lymphocyte invasion is reduced but macrophage penetration excessive, give a degree intermediate between autografts and homografts.

The important effect of these reactions is probably interference with the multiplication of Schwann cells and the formation of Schwann bands (*see* Plate XIV, fig. 13), since little evidence was seen of the actual blockage of the outgrowth of fibres within the grafted tissues of incorporated grafts. In addition to the shunting of pathways, maturation is likely to be delayed in fibres which are associated with few or abnormal Schwann cells. Indeed stored and fresh homografts at 200 days contained fewer large myelinated fibres than autografts or normal peripheral stumps (Sanders and Gutmann, 1942.)

In alcohol-fixed grafts the effects of shunting and interference with the Schwann cell-fibre association are maximal. The only Schwann cells associated with the outgrowing fibres before they actually reach and penetrate into the proliferation growing out of the peripheral stump are the cells which move out from the central stump along the outgrowing fibres (*see* Speidel, 1932 ; Holmes and Young, 1942). Moreover both the Schwann bands and the new fibres, pushing out from the stumps against the barrier of unremoved graft, must undergo considerable shunting and often actual

blockage. Thus it is not surprising to find that the degree of functional recovery attained after these grafts was always inferior to that following incorporated grafts, and was equal to that attained after unaided unions, in which similar processes are at work.

Different proportions of failures to recoveries among the groups of cases treated with different procedures were obtained. However, these are less easily correlated with the histological differences than the above functional results, probably on account of the small number of cases studied in the case of each procedure. Eight out of 8 end-to-end sutures, 8 out of 10 autografts, 6 out of 7 fresh homografts, 8 out of 8 Ringer-stored homografts, and 2 out of 4 alcohol-fixed grafts recovered reflex function. By contrast only 2 out of 14 cases of unaided union made a functional recovery.

The results of sensory recovery also did not reveal clear-cut differences between the various types of incorporated graft, probably because no animal was followed for longer than 200 days, and sensory recoveries may take place later than this date. However, sensory recoveries were obtained after every procedure except alcohol-fixed grafts and unaided unions. The time of onset of sensory recovery was much later than the time of motor recovery, a direct result of the anatomical situation, since the motor branches of the peroneal nerve are given off just below the knee, while the autonomous zone of the skin area supplied by this nerve is on the dorsum of the foot.

On the small amount of evidence presented it appears that end-to-end sutures recover sensation more quickly than grafts. Three sutures recovered at 124, 124 and 159 days. The graft recoveries occurred at 172, 174, 174 and 185 days, and there were three recoveries which were incomplete and progressing at 200 days.

The difficulties in the application of the results of such animal experiments to man have been discussed by Sanders and Young (1942). The autografts in the present series were all less than 4 mm. in diameter, and it may be that to be successful in man, autografts must be either small or else cable grafts (*see* Sanders, 1942). Whether thickness of graft is a decisive factor is not known, although the experiments of Maccabruni (1911), Bielschowsky and Unger (1917), and Bunnell and Boyes (1939) suggest that in thick grafts the centre of the graft does not carry many new fibres. There is no reason to suppose that long grafts are likely to be less successful than short (Sanders and Young, 1942).

The case of homografts is less certain. There are undoubtedly differences in tissue reactions in man and rabbit, and it is not known how far the

unfavourable reactions whose effects have been described would be duplicated in man. Only experiment can show this, and the method has never been thoroughly tried out in man (*see* Sanders, 1942), although there are indications (Duel, 1934) that small, thin homografts might be successful. The fact that fibres were irregularly distributed and only occasionally reached a large diameter in the thin homografts of the rabbit's tibial nerve, suggests that the factor of size may be important in the case of homografts. Small homografts, and perhaps cable grafts, where the factor of size is not operative, would afford the clearest evidence of the possibilities afforded by homografting in man.

The present experiments emphasize the need to use in man only those methods which, in addition to conducting the greatest number of fibres to the periphery, cut down shunting of pathways to a minimum, and favour the maximum of maturation of fibres within the regenerated nerve trunk. As there are more fibre-types in the nerve-trunks of man than in the rabbit, and the functions to be restored are correspondingly more delicate, the use of such methods as alcohol-fixed grafts, where the effect of the above factors is at a maximum, is definitely contraindicated. In the choice of a method to repair a particular nerve defect in man, a compromise must be made between the necessities of the anatomical situation, and the amount of recovery needed to give the patient a sufficient recovery from an economic point of view. The success of auto- and homografts in animals and of thin autografts in man (*see* Sanders, 1942) indicates that there are some situations in which an incorporated nerve graft may be of considerable value.

Summary.

(1) The peronal nerve of the rabbit was cut in the thigh and repaired by (*a*) unaided union of stumps ; (*b*) end-to-end suture ; (*c*) various types of nerve graft. The time of onset of motor recovery in the muscles of the small peroneus group was determined by observing the return of reflex spreading of the toes. An estimate of the final degree of recovery attained after different procedures was made by plotting the amplitude of toe-spreading on an arbitrary scale—the " spreading index." Recovery of pain sensibility in the skin of the dorsum of the foot was also studied, and the histological conditions of the various grafts as late as 200 days after operation.

(2) Eight out of 8 cases of end-to-end suture recovered toe-spreading 56-85 days after operation ; 8 out of 10 autografts in 51-98 days ; 6 out of 7

fresh homografts in 70-125 days; 8 out of 8 homografts stored for 7, 14, or 21 days in Ringer at 2°C. before insertion, in 61-117 days; 2 out of 4 dead alcohol-fixed grafts in 124 and 142 days ; and 2 out of 14 unaided unions in 117 and 162 days.

(3) After no procedure was the normal amplitude of spreading restored. End-to-end sutures and autografts showed after recovery the amplitude of spreading which came nearest to normality. Three fresh homografts and two stored homografts recovered spreading of somewhat smaller amplitude. Spreading of the least amplitude was shown by alcohol-fixed grafts and unaided unions.

(4) Sensory recovery on the dorsum of the foot occurred in three end-to-end sutures at 124 (twice) and 159 days: on one autograft at 174 days; in two fresh homografts at 172 and 185 days, while in another it was incomplete at 200 days ; in one stored homograft at 174 days, while in two others it was incomplete at 200 days ; recovery failed to appear before 200 days in all alcohol-fixed grafts and unaided unions.

(5) The structure of the various grafts at 200 days showed the effect of the tissue reactions which sometimes accompany the earlier stages. Autografts were indistinguishable from normal peripheral stumps. Fresh homografts showed fibrotic zones and often spaces with macrophages ; the extensive lymphocytic infiltration, often found in the early stages, had disappeared by 200 days. Stored homografts showed some fibrosis, but otherwise resembled normal nerve, there being no trace of the excessive macrophage invasions present in the early stages. Alcohol-fixed nerves showed evidence of destruction and replacement by the host tissues, and consisted of connective tissue masses traversed by new fibres in irregular bundles. They resembled the strand connecting the stumps in unaided unions.

(6) Nevertheless, at 200 days grafts, peripheral stumps, and the strand of tissue connecting the stumps in unaided unions all contained myelinated nerve fibres. These were more numerous in normal peripheral stumps, autografts, and Ringer-stored homografts than in fresh homografts, alcohol-fixed grafts, or unaided unions. Fibres also attained a greater diameter in autografts than in homografts, where the largest fibres were restricted to the edges of the graft. The smallest fibre-size was attained in alcohol-fixed grafts.

(7) In the two auto- and one homografts in which recovery failed the grafts were reduced in diameter, contained many macrophages, and only a few thin nerve fibres.

(8) This study of functional recovery following nerve grafts shows that autografts can survive, become reinnervated, and be followed by as rapid and complete a recovery as after end-to-end suture. Homografts can also be followed by recovery, but this occurs a little later than in autografts and is not so complete—presumably owing to adverse tissue reactions. Previous storage of the graft, which reduces these reactions, promotes a more complete recovery, but does not make it occur significantly earlier. Alcohol-fixed grafts are replaced by the tissues of the host, and are followed by very late and poor recoveries, comparable to those obtained after the unaided union of stumps.

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DESCRIPTION OF PLATES.

All figures are of material taken from the hind limb nerves of the rabbit, embedded in paraffin wax through cedarwood oil. The stains used are indicated in each legend —e.g. (Bodian). Where counterstains have been used they are indicated as follows —e.g. (Bodian-Masson).

Abbreviations used in the plates.

ax. = axon
ax. e. = axon end-bulb
e. sch. t. = empty Schwann tubes
fib. = fibroblasts
f. sch. t. = Schwann tubes with fibres.
gr. = graft
lym. = lymphocyte
mac. = macrophage(s)
my. = myelin remains
pc. = peroneal central stump
pp. = peroneal peripheral stump
s. = sural nerve
str. = connecting strand, or "ghost" nerve
t. = tibial nerve
v. = blood-vessel.

PLATE XIII.

FIG. 1.—Reunion of peroneal nerve across a gap of 2 cm. made 191 days previously. Note bulbous central stump, peripheral stump with a "glioma," which is joined to the central stump by a thin strand. (598; left side.)

FIG. 2.—Portion of connecting strand in an unaided union of 180 days, showing new myelinated fibres looping and twisting about one another. (Flemming-Weigert.) (582a. 4. 1.)

FIG. 3.—Part of peroneus longus of an unaided union of 165 days which recovered electrical excitability but not reflex function. Amid atrophic muscle fibres there is a nerve trunk consisting of empty Schwann tubes. Another smaller trunk contains a few fairly thick nerve fibres. (Bielschowsky-Gros.) (557k. 4. 1.)

FIG. 4.—Small nerve trunk in the peroneus longus in an unaided union of 180 days which recovered reflex function. Many nerve fibres. (Bielschowsky-Gros.) (582d. 8. 1.)

FIG. 5.—Part of the same muscle as fig 7 showing two new fibres innervating a single muscle end-plate. (Bielschowsky-Gros.) (582d. 4. 3.)

FIG. 6.—Portion of homograft at 200 days. Spaces still containing macrophages. (Masson.) (537c. 4. 11.)

FIG. 7.—Portion of a homograft at 200 days showing fibrosis disturbing pattern of nerve. No macrophages. (Bodian-Masson.) 658e. 2 4.)

FIG. 8.—Portion of a stored homograft at 200 days. Note new fibres, less fibrosis than in fresh graft, a macrophage, blood-vessel, and an axon showing a club of growth. (Bodian-Masson.) (611i. 7. 17.)

PLATE XIV.

FIG. 9.—Portion of connecting strand 123 days after closure of a 36 mm. gap by unaided union. Note fibrous tissue, Schwann bands, a blood-vessel. (Masson.) (538d. 1. 3.)

FIG. 10.—Portion of the strand replacing an alcohol-fixed graft at 200 days. Irregular bundles of Schwann cells + nerve fibres running in a matrix of connective tissue (cf. fig. 9). (Bodian-Masson.) (602d. 3. 9.)

FIG. 11.—Portion of peripheral stump 8 mm. below an autograft made 64 days previously. Regular arrangement of Schwann bands, new fibres, macrophages. (Bodian-Masson.) (520b1. 5. 7.)

FIG. 12.—Portion of an autograft at 64 days to show Schwann bands and new fibres. The spaces containing macrophages are larger than in a normal peripheral stump (cf. fig. 11). (Bodian-Masson.) (520b. 5. 5.)

FIG. 13.—Portion of fresh homograft at 61 days, showing large spaces full of macrophages, which cause considerable deviation and branching of the fibres and Schwann bands (cf. figs. 11 and 12). The fibres are thinner than in an autograft. Scattered lymphocytes. (Bodian-Masson.) (640d. 3. 11.)

FIG. 14.—Portion of a stored homograft at 73 days to show accumulation of macrophages at one side of the graft. (Bodian-Masson.) (505a. 4. 9.)

PLATE XV.

FIG. 15.—Myelinated nerve fibres in the central stump 1 cm. above a plasma suture made 200 days previously. (Flemming-Weigert.) (670a. 1. 3.)

FIG. 16.—Myelinated fibres in the peripheral stump 1 cm. below a plasma suture made 200 days previously. Note fibres smaller than in central stump. (Flemming-Weigert.) (670b. 2. 2.)

FIG. 17.—Myelinated fibres in an autograft at 200 days. (Flemming-Weigert.) (671b. 2. 1.)

FIG. 18.—Myelinated fibres in a homograft at 200 days. Note large areas in which there are few or no fibres. (Flemming-Weigert.) (658b. 2. 1.)

FIG. 19.—Myelinated fibres in a stored homograft at 200 days. (Flemming-Weigert.) (602h. 3. 4.)

FIG. 20.—Myelinated fibres in the strand replacing an alcohol-fixed graft at 200 days. Most of fibres are small. (Flemming-Weigert.) (602b. 1. 1.)

THE GIANT CELLS OF BETZ, THE MOTOR CORTEX AND THE PYRAMIDAL TRACT: A CRITICAL REVIEW.

BY F. M. R. WALSHE.

I.—INTRODUCTION.

II.—THE GIANT CELLS OF BETZ AND OTHER PYRAMIDAL CELLS OF AREAS FA AND FB.

III.—THE RELATION OF THE BETZ CELLS TO THE MOTOR CORTEX.

IV.—THE BETZ CELLS, THE MOTOR CORTEX AND THE ORIGIN OF THE PYRAMIDAL TRACT.

V.—SOME CONSIDERATIONS ON THE FUNCTIONS OF THE MOTOR CORTEX.

VI.—GENERAL CONCLUSIONS.

REFERENCES.

I.—INTRODUCTION.

"There is, perhaps, no subject in physiology of greater importance and general interest than the functions of the brain, and there are few which present to experimental investigation conditions of greater intricacy and complexity. No one who has attentively studied the results of the labours of the numerous investigators in this field can help being struck by the want of harmony, and even positive contradictions, among the conclusions which apparently the same experiments and the same facts have led to in different hands. And when seemingly well-established facts of experimentation on the brains of lower animals are compared with those of clinical observation and morbid anatomy in man, the discord between them is frequently so great as to lead many to the opinion that physiological investigation is little calculated to throw true light on the functions of the human brain. These discrepancies appear less unaccountable when the methods of experimentation and the subjects of experiment are taken into consideration."—FERRIER. Introduction to "The Functions of the Brain," Second Edition, 1886.

When Holmes and Page May (1909) undertook their investigation of the exact origin of the pyramidal tract, they recorded that "little or no precise information can be obtained on the origin of the pyramidal tract in even the later editions of the most authoritative textbooks on the anatomy of the nervous system."

By making use of the reactionary chromatolysis (retrograde degeneration, *reaction à distance*) and the subsequent changes which occur in nerve cells after division of their axones, they sought to determine the cortical

cells which reacted thus after section of the corticospinal tract in the upper cervical region of the spinal cord, and might be considered therefore as the cells of origin of this tract. They performed hemi-section of the cord at the level of the first cervical segment in the cat, dog, lemur, macaque and chimpanzee, and these animals were sacrificed at periods ranging from 5 to 157 days subsequently, the cerebral cortex being then stained by the Nissl method and examined for cell changes. In addition, two human cases of severe traumatic lesion of the lower cervical cord were similarly histologically studied. In these circumstances they found the reactionary cell changes confined solely to the giant cells of Betz in the paracentral lobule and in the upper part of the ascending frontal (precentral) convolution, and they concluded that these cells are the sole source of the pyramidal fibres. To this conclusion, they added some inferences that did not arise directly from their studies, namely, that the Betz-cell-bearing area of the cortex corresponds to the excitable motor cortex, and that both are co-extensive with Brodmann's area 4 of the frontal cortex.

If the method of reactionary chromatolysis be a valid one for this purpose, that is, if we may assume that *all* the cells giving rise to pyramidal fibres undergo this reactionary change when the corticospinal tract is divided, then it seems that we must accept the view that the Betz cells alone give rise to this tract. In fact this view has been very widely accepted up to the present time.

Levin and Bradford (1938) have repeated these experiments in the macaque with almost identical results. They find retrograde degeneration in 81 per cent of the Betz cells of area 4, and also in some of the " ordinary large pyramidal cells " of this area. Adjacent to degenerated cells were to be seen cells of fairly normal appearance. The authors point out that the smaller Betz cells are not always readily distinguishable from the large pyramidal cells, and express the view that " Betz cell " might be used as a term to include all cortical cells of whatever kind that send axones to the spinal cord. They believe that about 20 per cent. of pyramidal fibres arise from Brodmann's postcentral areas, 3, 1, 2, 5, and estimate the total number of cells of origin of the pyramidal tract in *macacus* as about 31,000, of which some 6,000 are postcentrally situated. This last group presumably corresponds to the giant cells of the fifth layer of the post-central convolution in man, forming Economo and Koskinas' (1925) *area gigantopyramidalis postcentralis.*

This contribution provides an inkling of some of the difficulties that beset the attempt to attribute to the Betz cells the sole origin of the

pyramidal tract; namely, the uncertainties inherent in the identification of the cells so named. If our application of the title "giant cell" lacks precision or a generally accepted standard, then for us to assert that these cells alone give rise to the pyramidal tract is not to solve the problem of the origin of this tract, but to leave it still an open question. Indeed, our conception of the Betz cell is the crux, not only of this problem, but of several others of equal importance.

A study of the relevant literature shows, in fact, that the attribution to the Betz cells of the sole origin of the pyramidal tract is full of difficulties and unsolved questions. Some of these have long been apparent, but others have only recently come to light. Of the latter there is the striking discrepancy between the estimated totals of Betz cells in a single hemisphere (Campbell, 1905; Levin and Bradford, 1938; Lassek, 1940), and the total number of pyramidal fibres (Lassek, 1939, 1940, 1941, *a* and *b*, 1942). The ration between cells and fibres is as 1 : 40.

Difficulties of a physiological order have long been obvious, though of late years quite ignored. Thus, Horsley (1909) in his Linacre lecture pointed out (in a passage cited on page 431 of this review) that in that part of the precentral convolution wherein are represented the movements of the head, of facial expression, of deglutition and of articulate speech, there is a virtual absence of Betz cells. Even earlier, Campbell (1905), the pioneer of cortical cytoarchitectonics, had drawn attention to the absence of "true giant cells" in this region, though he had noted the presence of "scattered nests of large pyramidal cells, which differ from those common to the whole precentral cortex in being more attenuated and in having longer processes and larger and more distinct chromophilic elements."

Even in the region wherein hand and digit movements are represented, the Betz cells are relatively scanty (as figs. 5 and 10 reveal) though this region of representation is an extensive one. In all these circumstances, it becomes difficult to credit the Betz cells with the exclusive origin of the corticospinal and corticobulbar fibres.

This mention of corticobulbar fibres, made by Horsley, draws attention to the fact that experimental section of the cervical cord can give rise to reactionary chromatolysis only in that part of the precentral convolution in which movements of the limbs and trunk are represented. Yet the motor cortex must be taken to include the representation of the other movements enumerated by Horsley, a representation which is of the same physiological order as that of the movement of the limbs and trunk. The

projection fibres from this representation run to motor nerve nuclei in midbrain, pons and medulla, and therefore it is essentially the relation of the Betz cell to what the clinical neurologist speaks of as the upper motor neurone that is in question.

Horsley's pertinent comment, to which attention was drawn in these pages by the present writer in 1935, attracted no attention, and this also has so far been the fate of the more fully reasoned objections on the same lines formulated by Economo and Koskinas in their important study of the cytoarchitectonics of the human cerebral cortex (1925). These authors draw attention to the fact, amply demonstrated by them, that the Betz cells are largest and most numerous where the extremely limited repertoire of simple movements of the muscles of the pelvis, perineum and lower limb are represented, but fewest and smallest where the fine but highly co-ordinated movements of the face and mouth, including those of articulate speech, are represented on the precentral convolution. The region representing hand and finger movements occupies the mean between these extremes, and they regard these facts as making it appear highly improbable that the Betz cells are the sole cells of origin of the corticospinal (and corticobulbar) fibres.

It becomes clear, then, that we need the precisest possible notion as to what constitutes a Betz cell before we can usefully consider its relation to the upper motor neurone, or say what role this cell plays in the formation and functions of the motor cortex. We must know whether the Betz cell is a specific morphological entity with functions peculiar to it, or whether it is simply the largest member of the large family of pyramidal cells. Involved in all these questions is the further one, at present a somewhat controversial question, as to what we refer to when we speak of the motor cortex. In the ensuing pages it is proposed to discuss these questions.

II.—THE GIANT CELLS OF BETZ AND OTHER PYRAMIDAL CELLS OF AREAS FA AND FB.

(*1*) *Size and Appearances.*

"Die Physiologie hat auf allen Gebieten ihr sicherstes Fundament in der Anatomie. Wer physiologische Lokalisationsarbeit leisten will, wird daher seinen Forschungen die Ergebnisse der histologischen Lokalisation zugrunde legen müssen. Und mit mehr Recht als je darf heute an das vom Altmeister der Hirnforschung, Bernard Gudden, schon vor drei Jahrzehnten gegenüber einem einseitigen und gefährlichen Extirpations-spezialistentum gesprochene Wort erinnert werden: 'vor einer zweifellos bewiesenen anatomischen Tatsache verliert jedes physiologische Resultat, welches mit derselben in Widerspruch steht, seine Bedeutung . . . Zuerst

also Anatomie und dann Physiologie, wenn aber zuerst Physiologie, dann nicht ohne Anatomie."—(BRODMANN. Vergleichende Lokalisationslehre der Grosshirnrinde. 1909).

Gudden's aphorism is very pertinent to our present review of the available facts of anatomy concerning the Betz cell in view of the edifice of hypothesis that has been built round the assumption that this cell alone gives rise to the pyramidal and corticobulbar fibres, and that it alone is the significant cell of the motor cortex.

In this chapter there are two anatomical questions to be considered, namely, that of cell types in the relevant cortical region, and that of their grouping and distribution therein. The last study is that now known as cytoarchitectonics. Our sources include the studies of Campbell (1905), Brodmann (1909, Economo and Koskinas (1925) and Conel (1939, 1942). Reference must also be made to the work of C. and O. Vogt (1919) because, though this conflicts with that of all the other authorities named, it has been made the basis of recent experimental cortical physiology on the motor and so-called " premotor " cortex.

Not only have the various types of nerve cell in the cortex been described and classified, but these observers have also described the lamination of the cortex and its local variations. Brodmann divided the cerebral cortex into regions, and each of these into areas. The *region* with which we are concerned is known as the *regio praecentralis*, and it has been divided, on the basis of cellular and laminar peculiarities, into two areas. For these, each authority has coined his own nomenclature, and as it is necessary to use them all on occasion, they are given here. They are (1) the area immediately anterior to the fissure of Rolando:

Campbell's Area precentralis
Brodmann's Area 4
Economo and Koskinas' Area FA (including FAγ)
C. and O. Vogt's Area 4 (subdivided into a, b and c)

(2) the area lying anterior to the preceding:
Campbell's Area precentralis intermedia
Brodmann's Area 6
Economo and Koskinas' Area FB
C. and O. Vogt's Area 6 (subdivided into 5 subareas)

Together these two areas make up the agranular frontal cortex, so called because within it the two granular layers, II and IV, of the cortex are virtually absent. From the IInd to the Vth layers inclusive the nerve

cells are all of pyramidal type, and the cortex here is said to have undergone "pyramidisation." Fig. 1 gives these two areas as delimited by Campbell, by Brodmann and by Economo and Koskinas. Foerster has also

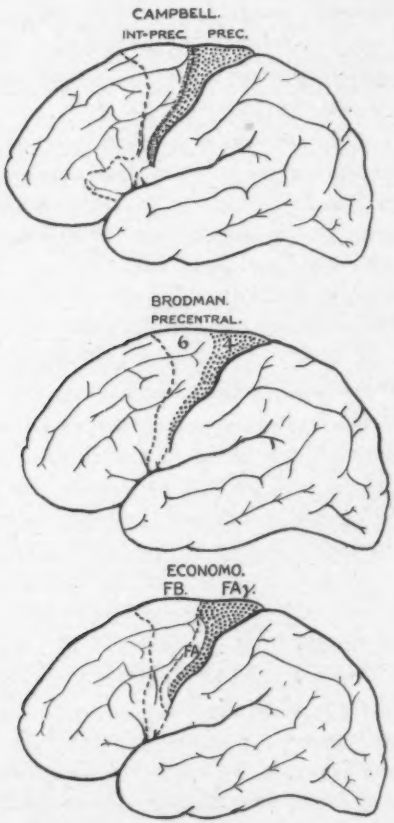

FIG. 1.—The maps of Campbell, Brodmann and Economo and Koskinas on which the two component areas of the agranular frontal cortex (the regio præcentralis) are depicted.

drawn up a map of cortical areas for man, but this is not based on direct histological study and is simply a copy of the cortical areal map of *cercopithecus*, drawn up by C. and O. Vogt, adapted to a diagram of the human cerebral cortex.

Before proceeding to a detailed description of the cell types and cell arrangements in areas 4 and 6, we may make the general statement that in these areas we find very numerous pyramidal cells covering a wide dimensional range from the smallest pyramidal cells at one extreme to the so-called giant cells of Betz at the other. These have been classified into a number of types, which tend to overlap dimensionally. Thus the smallest Betz cells are no larger than the largest of the "large ordinary pyramidal cells." This last fact suggests that size alone can hardly be a wholly satisfactory criterion of identity for the Betz cell, and when we come to examine the dimensional standards given by the numerous histologists who have studied the Betz cells we find that they vary very widely, and give the impression that the identification of the cell commonly so named, and known alternatively as the giant cell, must be a far less simple matter than is commonly assumed.

These dimensional standards are as follows:

Betz,	40 to 120 μ long by 50 to 60 μ broad
Bevan Lewis,	30 to 96 μ long by 12 to 45 μ broad
Hammarberg,	80 μ long by 40 μ broad
Brodmann,	106 μ long by 53 μ broad
Economo and Koskinas,	50 to 120 μ long by 25 to 60 μ broad
Conel (one month child)	34 to 82 μ long by 10 to 23 μ broad.

Economo (1929) states that all pyramidal cells larger than 50 by 25 μ are to be called giant cells, and records that pyramidal cells of 65 by 30 μ are to be found in layer IIIc of area FB, while in the one-month child Conel finds cells of 37 by 12 μ in layer V of the same area.

We may ask whether these varying criteria merely reflect the individual differences that are known to obtain, or whether they express actual difficulties in identification, or rather in differentiation from other large pyramidal cells. As will appear there can be no doubt that the latter factor plays a large part in these differences of standard. In the adult these figures give an extreme range of size for Betz cells from small cells of 30 to 12 μ to large cells of 120 by 60 μ. They reveal how loose is the appelation "giant cell" and what an exaggerated impression of the distinct individuality of this cell it conveys.

Size, then being plainly a very unsatisfactory criterion of identity, we turn to the microscopic appearance of the Betz cells as revealed by Nissl staining, or by silver-impregnation methods that reveal the silhouette of the cell body and processes. Even here we do not find any *absolute*

criterion of difference between Betz cells and the largest pyramidal cells.

We find the most exhaustive comparative study of pyramidal cells of all types in the human cerebral cortex in the investigations of Economo and Koskinas, who give two standards of classification: one purely in the matter of the shape of the cell body, the other based upon Nissl and silver appearances.

(*i*) *According to Form.*—In this grouping the ratio H $\frac{B}{2}$ is adopted, where H is the height and B the breadth at the base.

(*a*) H $\frac{B}{2}$ is as 1 : 1 "plattgedrückte Pyramidenzellen."
(*b*) H $\frac{B}{2}$ is as 2 : 1 "flachdreieckige Pyramidenzellen."
(*c*) H $\frac{B}{2}$ is as 3 : 1 "mittelschlanke Pyramidzellen."
(*d*) H $\frac{B}{2}$ is as 4 : 1 "schlanke Pyramidenzellen."
(*e*) H $\frac{B}{2}$ is as 5 : 1 "überschlanke Pyramidenzellen."

Of greater interest in our present connection is the second grouping,

(*ii*) *According to Appearances in Stained Sections.*—(*a*) *Small pyramidal cells* $\frac{H}{B} = \frac{10 \text{ to } 15}{7 \text{ to } 10}\mu$. With a small oval nucleus and a single satellite cell.

(*b*) *Middle-sized pyramidal cells* $\frac{H}{B} = \frac{20 \text{ to } 30}{10 \text{ to } 20}\mu$. With a round nucleus near the base, nucleolus and one or two satellite cells.

(*c*) *Large pyramidal cells* $\frac{H}{B} = \frac{30 \text{ to } 50}{15 \text{ to } 20}\mu$. With a large clear nucleus, a dark nucleolus and two or three satellite cells.

(*d*) *Giant cells* ("*Riesenpyramiden*" or "*einfache Riesenpyramidenzellen*")

This category, not found elsewhere than in Economo and Koskinas' work, is scarcely larger than the preceding one: viz $\frac{H}{B} = \frac{50 \text{ to } 60}{25}\mu$. These cells however, are more massively built, and have a cytoplasm in which marked Nissl granules are seen. The nucleus is in the centre of the cell and the nucleolus is large. Of these simple giant cells the authors observe "Es ist oft schwer zu sagen, was man noch als Riesenzelle zu bezeichnen hat, weil sich alle Übergange von der einen zu der anderen Art vertreten finden," and again "Im Einzelfälle oft schwer is to unterscheiden, zu welcher Gruppe das einzelne Individuum gehört, da alle möglichen Übergansstufen zu finden sind."

It is noteworthy that these cells are to be found in *all* parts of area FA in layers IIIc and V.

(*e*) *Betz giant cells* (*"Betzsche Riesenpyramiden"* or *"Kolossalzellen"*).—These include the largest nerve cells in the entire cerebral cortex, but the smaller members of the group are no larger than cells of the two preceding categories. They range in size from $\frac{H}{B} = \frac{60 \text{ to } 120}{40 \text{ to } 60} \mu$, though according to other writers cells of even smaller dimensions are named Betz cells. These cells have a typically tall build, and in outline vary somewhat, being described as pyramidal, pyriform or like a burgundy bottle. On the buried surface of the precentral convolution where they lie in the fissure of Rolando, they tend to be less well-formed, and distorted in outline. They lie almost exclusively in layer V, though occasional specimens are to be seen "disloziert" in layers IV and IIIc. They are confined to area FAγ, Their dendrites are stout and knotted in appearance, so that by silver impregnation methods the cell and its processes resemble a tree with roots and branches. This appearance is beautifully illustrated in fig. 2, taken from Conel's atlas of the cortex in the one month child. The cell body contains numerous large Nissl granules (from 4 to 6 μ in diameter) and stains darkly, so that in stained sections the cells can be seen as darker spots to the naked eye. The nucleus is a clear bladder-like structure of some 25 μ diameter, and contains a dark nucleolus that may measure from 4 to 7 μ in diameter. From 5 to 6 satellite cells accompany each Betz cell. Lying in close proximity to these cells are very numerous simple giant cells and large pyramidal cells, and speaking of them Economo and Koskinas say "Naturlich finden sich alle Übergange in Grösse and Form von diesen Riesenpyramiden einerseits zu den Betzschen Kolossalzellen, andererseits, wieder nach ruckwärts zu den gewöhnlichen grossen Pyramidenzellen." Betz cells are found in small nests of from 3 to 8, and these together form larger aggregations, as Betz (1874), Bevan Lewis (1878) and Campbell (1905) have all noted. Thus, even within area FAγ they do not form a continuous field.

From this classification it appears that Economo and Koskinas have felt it neessary to formulate two categories of giant cell, differing not qualitatively, but in degree of size, massiveness of form, size and abundance of Nissl granules, and in stoutness of processes. The larger group (Betz cells) are said to be restricted to area FAγ and to layer V, the simple giant cells are found over the whole of area FA, and in two cortical layers, IIIc and V. In the former layer they are also found at the hinder ends of the frontal convolutions where areas FA and FB meet.

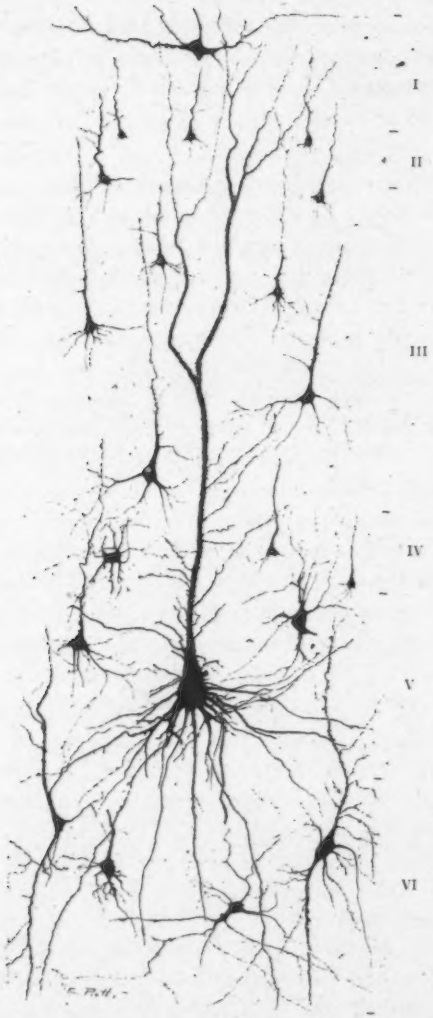

FIG. 2.—A camera lucida drawing of the cortex of the paracentral lobule stained by the Golgi-Cox method. Fig. 18 of Conel's Vol. II, on the cortex of the one-month child (Harvard University Press).

Classification thus provides us with three categories of large pyramidal cell, Betz cell, simple giant cell and large pyramidal cell, but it seems clear that every possible transition form between the members of this conventional grouping is to be seen, not only in the adult cortex as reported by Economo and Koskinas, but also in the infant cortex as recorded by Conel (1942). At one extreme we have the Betz cell with its numerous large Nissl granules, at the other the slenderer large pyramidal cell which only exceptionally contains distinct Nissl granules, but the series is continuous, and we can no longer accord the Betz cell the exclusive position we have hitherto given it as a specific entity with functions exclusive to itself. The Betz cell is no more than the largest and most massive member of the large group of pyramidal cells. This is, indeed, the conclusion to which Economo and Koskinas arrive, and they state that "dieseverschiedene Zellen also nicht anderes als durch ihre Grösse unterschiedene Individuen ein und derselben Zellart sind" (p. 290).

For purposes of description, classification is necessary, but having once made our groups, we are too ready to assume that we have discovered essential qualitative distinctions that may have no reality in nature. It may be suggested that this has been the case with the giant cell of Betz, and the Russian histologist could have chosen no more striking word than "giant"—with its emotive background of nursery mythology—to impress us with a sense of the exclusiveness of the cell he so described, and to perpetuate that impression despite the accumulating weight of evidence that it has no real foundation in nature.

(2) *Distribution in Areas FA and FB.*

If the microscopic study of stained pyramidal cells has failed to establish the specificity of the Betz cell, it remains to be seen whether the distribution of this cell within the cortex confers exclusive qualities upon it. If for the moment we exclude from consideration large pyramidal cells and simple giant cells that, as seen in Nissl stained sections, may present difficulties in classification, there remains a considerable group of what all would regard as Betz cells. These are the larger members of the group so named. In man, these are found only within that posterior part of area FA that Economo and Koskinas call FA γ or the *Area gigantopyramidalis precentralis.*

The limits of this area are fully depicted in fig. 3, which is made up of figures 133*a* and 133*b* of Economo and Koskinas superimposed. The figure also gives the limits of the whole area FA. It will be seen that at the level

of the third frontal convolution the Betz cell distribution has sunk entirely into the depths of the fissure of Rolando. The lower limit of Betz cell distribution is reached at a distance of from 2 to 4 cm. above the fissure of Sylvius.

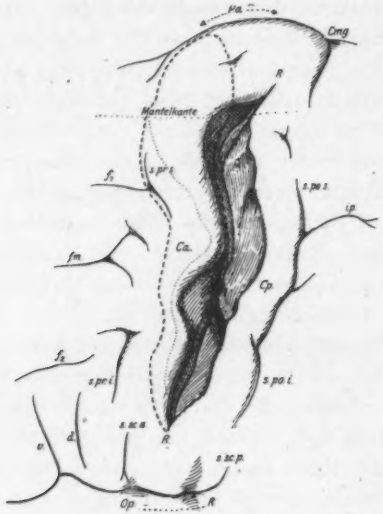

FIG. 3.—Economo and Koskinas' Fig. 133*a*, with the limits of areas FA and FA γ superimposed from fig. 133*b* (Economo and Koskinas, p. 522). The paracentral lobule is represented as though in the same plane as the convexity of the hemisphere, and the mesial fissure is represented by a dotted line and the word "Mantelkante," The fissure of Rolando is opened so as to show its floor. Area FA is demarcated by an interrupted line, and the anterior limit of area FAγ by a dotted line.

It might easily be concluded from the linear boundaries given to the Betz cell distribution, that these boundaries were clearcut and unequivocal. This is undoubtedly true of the posterior boundary which lies almost at the bottom of the fissure of Rolando, some 2 mm. from its floor and on the anterior wall of the fissure. The limits of these cells on the mesial aspect of the hemisphere in the paracentral lobule are also fairly clear, but the anterior border of the Betz-cell-bearing area is quite another matter. As we trace the Betz cells forwards from the fissure of Rolando towards the anterior border of area FAγ, they diminish progressively in size and their differentiation from simple giant cells and from some large pyramidal cells becomes increasingly difficult. The simple giant cells are found over the whole of area FA in layers IIIc and V. The anterior border

of Betz cell distribution is a sharp one only if we take the most anterior cell we detect in a section and call that a sharp border, but if we take the field of Betz cells as a whole there is no such border. In the one month child, Conel confirms the transitional passage from Betz-cell-bearing to Betz-cell-free areas. He says the decrease in cell size "is so gradual that there is no abrupt boundary between Betz cells and the extra large pyramidal cells in layer V, so that it is impossible to say where the giant pyramidal cells end and the extra large pyramidal cells begin . . . The cells and their dendrites gradually decrease in size towards the anterior wall of gyrus centralis anterior, but even here some of them are as large as the largest cells in the posterior wall of the gyrus. On the basis of cell size it is difficult to say where area FAγ ends and FA begins" (p. 12).

Again "there is no abrupt change from giant cells to extra large pyramidal cells therefore it is impossible to say where the one type ends and the other begins" (17). In short, the anterior limits of the Betz-cell-bearing area do not admit of linear or precise definition.

Economo and Koskinas' placing of the anterior fringe of Area FA forwards of that of FA$_\gamma$ is explained by the fact that they have delimited their cortical area, not in respect of a single cellular element, but in respect of the "Gesamtbild" of the area; that is of all the features of all the cortical layers. Comparison shows that their area FA is slightly more extensive than Brodmann's area 4, an indication that cortical map-making is not an exact process, but a matter of broad distinctions and approximate estimates.

Within the generally accepted area of their distribution, the arrangement of the Betz cells presents certain characteristic features. In a recent study, Lassek (1940) finds that in an estimated total of 34,000 in a single hemisphere, 75 per cent. are to be found in the mesial third of the Betz-cell-bearing area, 17·9 per cent. in the middle third, and only 6·6 per cent. in the lower third (*see* fig. 10). Also, of the total, not less than 82 per cent. are buried in the anterior wall of the fissure of Rolando, only 18 per cent. lying on the free surface of the convolution. Other numerical estimates of these cells are Campbell's of 25,000 for man, and Levin and Bradford's of 31,000 for macacus, of which they find 6,000 in the postcentral convolution. From what has been said of the difficulties inherent in a precise identification of the Betz cell, these estimates must present a considerable margin of potential error. It has already been mentioned that the largest Betz cells are found in the paracentral lobule, the smallest at the anterior fringe of their distribution and in the lower end of the precentral convolution:

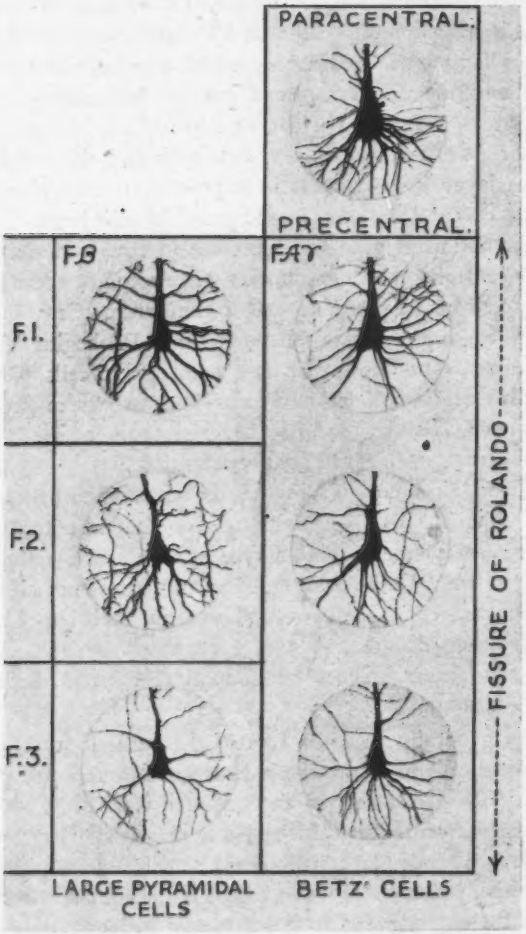

FIG. 4.—Drawings of Betz cells and large pyramidal cells in layer V of area FA and area FB. The cells are all placed within a conventional scheme that represents the fissure of Rolando, the paracentral lobule and precentral gyrus. F1, F2 and F3 represent the three frontal gyri, and the cells are placed according to their actual position in the cortex. The diagram shows the diminishing size of the cells as we pass from the upper to the lower part of the cortical surface. These cell drawings are from Conel's (Vol II) figs. 18, 22, 26, 30, 34, 36 and 42. They reveal the large dimensions of the large pyramidal cells of the posterior part of area FB and their general resemblance in form and proportions to the giant cells of area FA$_{\gamma}$.

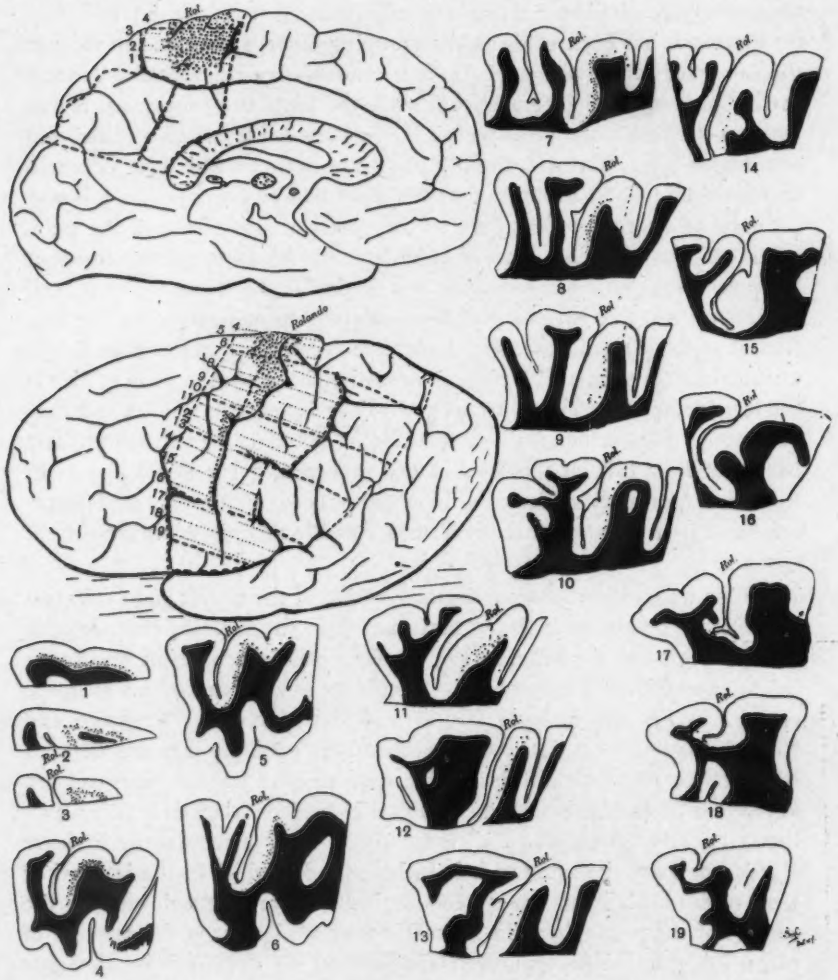

FIG. 5.—Campbell's plate IX. It illustrates the distribution of the giant cells of Betz, which in the cortical map are marked by dots, and by dots also in the sections of the cortex, which are numbered in correspondence with the map. It will be seen that the majority of Betz cells lie in the anterior wall of the fissure of Rolando. In the original plate, the situation of cellular changes associated with tabes dorsalis in the postcentral gyrus was indicated by crosses. These have been deleted as not relevant, and for the sake of clarity.

that is, where they are largest they are most numerous, least numerous where they are smallest.

Reference has been made to the grouping of Betz cells, and in view of the suggested identification of the Betz-cell-bearing area with the " motor cortex," it is interesting to note that while the latter is a continuous region with no constant silent areas within it, the Betz cell is not distributed in a continuous layer, but in a number of groups between which lie Betz-cell-barren areas. These groups have been described by Campbell as follows: (*a*) nests of enormous Betz cells in the posterior two-thirds of the paracentral lobule; (*b*) dense clusters of cells at the broad upper extremity of the precentral gyrus just lateral to the border of the hemisphere; (*c*) cell clusters on the free surface of the gyrus at the posterior end of the first frontal gyrus; (*d*) cell clusters at the level of the superior genu of the fissure of Rolando; (*e*) smaller cell clusters immediately below the genu. This is the lowest important and constant group, but, lower, two smaller and variable groups may be found. Between groups (*d*) and (*e*) is an area constantly barren of Betz cells at the level of the annectant gyrus of the fissure of Rolando. Campbell's Plate IX, here reproduced, shows the total distribution of Betz cells on the cortical surface and in sections of the precentral gyrus.

When we come to consider the distribution of the *simple giant cells* and of the *large pyramidal cells,* we find that while the superior and posterior limits of this are the same as for the Betz cells, the anterior and lower limits extend over a larger area. Simple giant cells are found over the entire area FA and in layer IIIc as well as in layer V. Economo and Koskinas say of them that " wir sprechen aber solche Zellen trotzdem als Riesenzellen an, wenn did durch ihre unmittelbare Lage zu den anderen kolossalen Betzschen Zellen und durch ihre übrigen Merkmäle sich als zu ihnen gehörig erweisen . . ." (page 63). Their arrangement in layer IIIc is not quite the same as it is in layer V, for while in the latter they tend to diminish in size as we follow them forwards and down over the surface of the hemisphere, in layer IIIc they are largest at the meeting of areas FAγ and FA, and even trespass on to area FB in the pars triangularis of the third frontal convolution. (cf. fig. 7.)

The large pyramidal cells extend even further forwards well into area FB, and in layer IIIc reach their largest dimensions in this area. Further, in layer V, the large pyramidals become more numerous at the lower part of area FAγ, and they seem to substitute for the Betz cells which disappear here from the cortex. Economo and Koskinas state that

"dieses grossen und ganz grossen Pyramidenzellen sind speziell in der Gegend des Handzentrums und auch besonders in den ventralen Teilen der vorderen Zentralwindung in ausserordentlichen Anzahl und

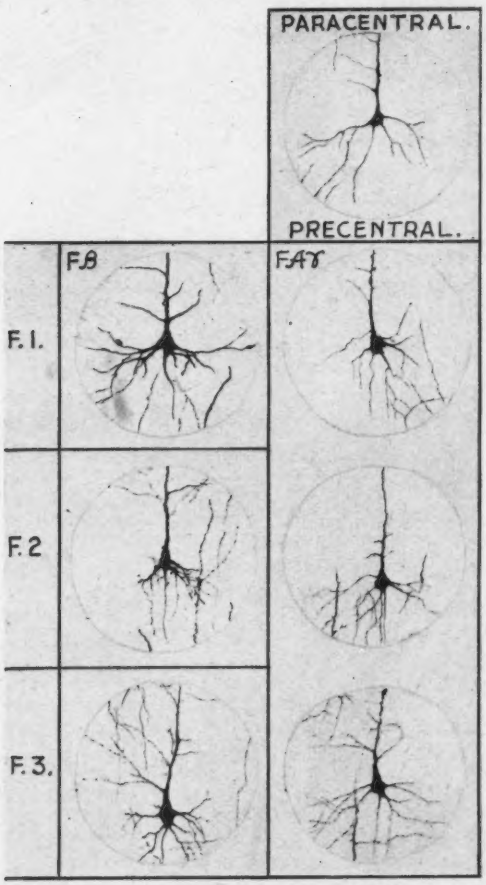

FIG. 6.—Drawings of large pyramidal cells in layer IIIc of area FAγ and area FB. They are arranged on the same topographical plan as in fig. 3, and are taken from the same drawings in Conel's volume II. It will be seen that the large pyramidal cells are larger in area FB than in the paracentral lobule and area FA γ.

Grösse vertreten, also gerade da, wo die Betzschen Riesenzellen beinahe fehlen. Dies legt den Gedanken nahe, dass hier vielleicht eine ganz

bestimmte Beziehung zwischen diesen Zellen verschiedener Grösse bestehen konnte." Between these large pyramidals and the Betz cells, they add, "alle möglichen Übergange und Zwischenstufen" are to be found, and they deem it likely that while the Betz cells are functionally related to large and simple movements of trunk and lower limbs, the more numerous large pyramidals serve a like role in respect of the small, finely co-ordinated movements of head and upper limbs.

Prominent as are these large pyramidal cells in layer V of area FA, they are an even more striking feature of layer IIIc, of which in area FB they form the most characteristic feature. So well do they stain that in Nissl sections they can be seen by the naked eye in area FB as a dark line. They vary in size from 35 to 80μ tall and 20 to 30μ broad at the base, and they really come within Economo and Koskinas' standard of size for simple giant cells. They are the largest pyramidal cells in the cortex after the Betz cells. Their apical dendrites may be followed towards the surface of the cortex for as far as from 100 to 120μ, and as Economo and Koskinas' figure shows (fig. 7*a* and *b* below) they are largest at the hinder

FIG. 7 A. FIG. 7 B.

FIG. 7, A and B.—Economo and Koskinas' figs. 79 and 74 respectively. A represents the distribution of giant cells in layer V. B represents the distribution of the large pyramidal cells of greatest size in layer IIIc.

end of the first and second frontal convolutions. Definite Nissl granules are only exceptionally seen in them, but they have a large clear, centrally situated nucleus, a deeply staining nucleolus and two or three satellite cells. As many as eighteen of these large cells may be seen in 0·1 c.mm. of tissue, a greater number than we find of Betz cells in the same sized unit.

It has been necessary to go into this detail concerning the various types of pyramidal cell in areas FA and FB to show that the facts in connection with them are far more complex than we may gather from the brief accounts commonly given. Both areas FA and FB are rich in large pyramidal cells. In layer V the size of these diminishes as we trace them forwards, and as they become smaller they lose progressively the features we have learned to look for in the Betz cell, but the change is a progressive and not a sudden one. In layer IIIc (and to a lesser degree in IIIb) the simple giant cells spread more widely than in layer V and cover the whole of area FA, but the large pyramidals tend to increase in size as we pass from FA to FB, and reach their maximal dimensions just over the border of the latter area, then again decreasing in size as we pass forward in the direction of FC. FA and FB differ most obviously in the disappearance of Betz cells in the latter and in the great development of large pyramidal cells in layer III of FB. In brief, the resemblances between areas FA and FB are greater than their differences and the border between them is characteristically lacking in sharpness, at least as far as layer V is concerned. It is the "Gesamtbild" of each area that justifies it being regarded as distinct, and it is in virtue of the "Gesamtbild" of area FA that Economo and Koskinas postulated an anterior Betz-cell-free part of area FA, the Betz-cell-bearing part being known as FAγ or the area gigantopyramidalis precentralis.

So far, we have discussed the human cortex only, but since apes of the Genera *cercopithecus* and *macaca* are largely used in the experimental physiology of this region, some reference to the cellular forms and cyto-architectonics of these animals is necessary. Brodmann has provided areal maps and cell descriptions of these. In these animals there are areas 4 and 6 homologous with those found in man, and together constituting an agranular frontal cortex. Area 4, the Betz-cell-bearing area in these types is of wider extent than in man and covers the precentral convolution. It is not, however, sharply demarcated from the area (6) lying immediately anterior to it, and it is useful to cite Brodmann's account of this border. Thus, he says (1909, p. 135.) "Ziemlich unbestimmte und schwankend ist die orale Grenze der Area gigantopyramidalis auf der Konvexität, da Feld 4 and 6 fliessend ineinander übergehen und da namentlich vereinzelte Betzsche Riesenzellen in 'solitärer' Anordnung bald mehr bald weiniger weit oralwärts zerstreut liegen, so dass die Festlegung der Übergangslinie rein subjektiv ist und nur aus zahlreichen Individualgehirnen gestimmt werden kann."

The map of cortical areas in *cercopithecus* that we owe to C. and O. Vogt presents a difficult problem of assessment, for it differs in essential characters from the cortical maps of all other observers, both of monkeys and of man. Whereas there is general agreement that cortical areas with few exceptions are not sharply separated, but merge into one another, and that each component cortical layer tends to have its own transition fringe, the Vogts maintain categorically that all cortical areas are typically separated by " haarscharf Trennungslinien ", that each area, physiologically considered, is equally sharply differentiated in respect of its functions, and that the dividing lines tend to be regular. For them the cortex is built on a chessboard or mosaic plan, both anatomically and physiologically.

Such a state of affairs has been found by no other observer before or later. Thus the pioneer, Bevan Lewis, observes that " no abrupt passage from one form of cortical lamination to that of another is ever seen in the convolutions of the vault. Changes in type are gradually assumed, and no distinct boundary exists to indicate an exact line of demarcation. The structure peculiar to one region gradually fades and blends with arrangements which foreshadow the architecture of adjacent realms, and thus we obtain transition regions." Modern research may have detected exceptions to this generalization, but they remain exceptions and are not found in the frontal lobe.

FIG. 8 A. FIG. 8 B. FIG. 8 C.

FIG. 8, A, B, C.—A represents Mauss's myeloarchitectonic map of cercopithecus, B is Brodmann's cytoarchitectonic map of the same type, and C is the Vogt's map for the same type.

Conclusions.

The agranular frontal cortex of areas 4 and 6 (FA and FB) is characterized by the presence of pyramidal cells of the varieties named in the preceding pages. These range from the giant cells of Betz, through the smaller simple giant cells and the large pyramidal cells to the small pyramidal cells. They reach their finest development in layers V and III (particularly IIIc), the Betz cell being virtually confined to layer V.

In view of the accounts given by the authorities we have cited, it becomes difficult to continue to regard the Betz cell as a specific morphological entity, standing in a class by itself anatomically and physiologically. At the fringes of its area of distribution where it is smallest in size it becomes extremely difficult to differentiate it from other pyramidal cells, and the erection by Economo and Koskinas of a new category of "simple giant cells" expresses this difficulty, and the repeated statement that there are present in layers V and III every stage of transition between the different categories emphasizes it. In the one-month child, Conel finds the same difficulty. In short, there is a cumulative body of evidence that the Betz cell is merely the largest category of the group of pyramidal cells and cannot on histological grounds be separated from them as something essentially different. That this separation has been widely assumed in the past cannot be doubted, for it is the real basis of the hypothesis that the excitable motor cortex of the physiologist consists of two components, of one of which the Betz cell is the sole nerve cell element. In a previous review on cutaneous sensibility (1942), the present writer took occasion to deplore the malign effect that nomenclature sometimes has on physiological thought, citing the words "epicritic" and "protopathic" as an instance. It may not be stretching the analogy too far to say that in the term "giant cell" we have a comparable example. As we have seen, the field of distribution of the Betz cells is a roughly triangular one, sharply bounded posteriorly by the line of the floor of the fissure of Rolando, mesially by the paracentral lobule and the superior border of the hemisphere, and anteriorly by the line given in Economo and Koskinas' map as forming the anterior limit of area FAγ. This anterior border is not distinct, because not only are the Betz cells fewer here, but their progressive diminution in size here renders them difficult of differentiation from other categories of large pyramidal cells (simple giant cells, largest ordinary pyramidal cells). At the apex of the triangle (its lower tip) in the depths of the fissure of Rolando and some 2 to 4 cm. above the line of the fissure of Sylvius, the Betz cells are very few and small.

The field of distribution of the simple giant cells, identical in form with that of the Betz cells, has the same superior and posterior border, but the anterior limits spread more widely to cover the whole of Area FA. These cells also are smaller and fewer all along this anterior border, so that the precise limits of their distribution in this direction has the same somewhat arbitrary character as that of the Betz cells. Finally,

we come to the largest ordinary pyramidal cells. These also show the same general distribution, but they spread still more widely anteriorly and encroach upon area FB. Yet while the giant cells diminish in number as well as in size as we reach the lower limits of their distribution, the large pyramidal cells here become more numerous. So that we find in the so-called "head area" that there are no Betz cells, but very numerous large pyramidal cells.

Thus speaking generally, we may say that there are three overlapping fields of large pyramidal cells, all with the same superior and posterior limits, but at the anterior limits varying in extent, smallest in the case of the Betz cells, slightly larger for the simple giant cells, but largest for the large ordinary pyramidal cells. These anterior limits are nowhere sharp for any of the three categories, Betz cells passing gradually into simple giant cells, and these into large pyramidals.

Within this general field of pyramidal cells of layer V, covering area FA and the adjacent posterior part of FB it is difficult to detect any inner dividing border separating qualitatively distinct components.

We have seen that the cortical areal map, such as that of Economo and Koskinas, is based expressly upon the "Gesamtbilder" of the areas it depicts. Within a given area, as these authors point out, each layer undergoes its own variations independently of those of the remaining layers. Thus one layer may extend unchanged into an adjacent area, while another undergoes considerable change within the limits of a single area. The areal map is therefore a composite affair. It strikes an average, as it were, between the competing claims of each of the six layers for representation. *It does not, therefore, strictly speaking, represent structure with anatomical precision.* When we come to equate a cortical physiological mechanism: e.g. the motor cortex, with the cyto-architectonics of the region in which we find it, we have to ask ourselves with what precisely are we to equate it, with the "area", or with the lamina?

In a given area, one or more of the cortical cell layers may have no part in the activities of the physiological mechanism we are considering. There are reasons for believing, for example, that the motor cortex and its projection the pyramidal tract are largely, if not wholly, based upon the fifth cortical lamina. This we have seen to possess a structural uniformity over an area wider than that of cortical area 4, namely, over the whole of area 4 and the adjacent posterior part of area 6 (that is,

FA and part of FB). *Therefore, in attempting to correlate function with structure, perhaps we should concern ourselves not with area 4, but with layer V in areas 4 and 6.* With these considerations in mind, it seems that in future we may have to direct our attention to a laminar physiology of the cortex rather than—as we have hitherto done—to an areal.

Possibly we shall have to consider layer V as constituting one physiological mechanism and layer III as providing the anatomical substratum of another. Moreover, it is well to remember when thinking in terms of cytoarchitectonics that function is not simply a matter of nerve cells, or of nerve cell bodies, but of the infinitely complex anatomical and physiological relations set up between these cells by means of their processes. It is at the synapse that occur the grading and interaction of excitation and inhibition, and synaptic arrangements occupy a place of primary importance in cortical structure and function. Therefore, the correlation of function and structure involves more than a study of cortical cytoarchitectonics.

In conclusion, an interesting sidelight on the probable physiological unity of cortical layer V over areas 4 and 6 is to be found in the observation recorded by Howe and Bodian (1942) to the effect that the virus of poliomyelitis shows a specific affinity for the nerve cells in these two areas. A glance at their Plate XXII suggests that this affinity is confined to some only of the cortical layers, apparently from III to V.

III.—THE RELATION OF THE BETZ CELLS TO THE MOTOR CORTEX.

"When the discovery of 'motor centres' first attracted attention, Dr. Bevan Lewis, as long ago as 1878, *showed that the precentral gyrus contained giant pyramidal cells in groups, and he mapped out this part of the cortex as being specialized for motion. Possibly because the groups of these giant cells did not correspond to the foci of representation as demonstrated by the method of excitation, and possibly also because (as he showed) there are areas of the motor cortex where no such cells exist, his observations did not attract the attention they deserved."*

"To include the whole efferent or motor area as determined by excitation we must take two of Campbell's regions, both his intermediate precentral and his precentral areas, though he wishes, apparently, the term 'motor' to be restricted to the latter. This suggested restriction of the term 'motor,' namely, because the giant pyramidal cells of Betz are to be found in only a certain (the major) portion of the precentral gyrus, cannot be justified, since it would exclude the motor centres for the face, larynx, pharynx, and eye muscles, as well as part of the representation of head movements."—VICTOR HORSLEY, Linacre Lecture (1909).

These two passages from Horsley indicate how widely physiological opinion moved after the date of Campbell's monograph, 1905. The pioneer experimentalists, unburdened by the exigencies of hypothesis,

were not greatly moved by the discovery of the giant cells because the incidence of these in the cortex did not correspond with the motor cortex as they had delimited it by electrical stimulation.[1] Campbell, preoccupied with the new field of research that he was exploring, was unwilling to regard as "motor" any cortical region that did not contain Betz cells. He had some grounds for this view, because Grunbaum and Sherrington's early observations on the excitable motor cortex had just been published and had shown that this region was more restricted than had been previously thought and was almost confined to the precentral convolution. Campbell noted that movements could be elicited from the cortex anterior to these limits only by strong faradism, and he therefore supposed that his intermediate precentral area constituted a more highly evolved motor mechanism corresponding to Jackson's first level. Yet, although Leyton and Sherrington's later (1917) experiments finally demonstrated the fallacy of Campbell's identification of the motor cortex with his precentral area: that is, Brodmann's area 4, his view still continues to have a large following, and many recent physiological studies are still interpreted on the basis of Campbell's erroneous view.

In the preceding pages passing references have been made to the motor cortex, and it was stated that Holmes and Page May had suggested that the Betz-cell-bearing area was co-extensive with the motor cortex. Such a view finds mention here and there in the literature of the past thirty years, but it has not been universally held, as the following citation from Brodmann (1913) clearly shows. "Die Regio praecentralis—ein ausgedehntes vor der zentral Furche gelegenes Gebiet, das wie bei Affen und Halbaffen festgestellte wurde in grossen ganzen der elektromotorischen Region entspricht. Sie umfasst die vordere Zentralwindung (Ca), die vorderen zwei Drittel des Lobulus paracentralis und einen Teil der angrenzenden I und II Frontalwindung. Strukturell ist sie augezeichnet hauptsachlich durch die Rückbildung der inneren Körnerschicht, die in der Tiefe des Sulcus centralis mit scharfer Grenze plötzlich eine Unterbrechung erfahrt. Sie setzt sich aus zwei agranularen Typen zusammen,

[1] It is noteworthy that in Ferrier's "Functions of the Brain," (Second Edition, 1886) there is no mention of the giant cells of Betz, while in Schafer's "Textbook of Physiology," 1900, in the chapter summarising cortical physiology, these cells obtain but a simple passing reference. It seems that up to 1905, experimental physiologists were pursuing their original studies of the motor cortex unhampered by any sense of responsibility for finding a specific function for the giant cell. It is not less striking that in all his work on the cerebral cortex, Sherrington has never assumed this responsibility.

der Riesenpyramidentypus (4) und der agranularen Frontaltypus (6), die oben geschildert sind" (p. 206). A similar view is expressed by Economo and Koskinas.

This point brings us sharply against a controversial issue of the past decade: namely, as to what we refer when we speak of the "motor cortex." Therefore, before we proceed further, we must seek to solve the conflict of definition that is seen in recent literature. That the present writer has already made one unavailing attempt at this (Walshe, 1935) should not deter us from a further reconsideration, since so much turns upon a generally accepted reference for the term "motor cortex."

If we trace the history of cortical stimulation experiments from their early days to the final authoritative delimitation of a motor cortex by Leyton and Sherrington (1917) in the chimpanzee, orang and gorilla, we find that the cortical region from which movements (exclusive of those of the eyes) can be elicited by electrical stimuli becomes more precisely defined and narrowed down until we reach the motor cortex of Leyton and Sherrington, delimited by threshold stimuli applied for known minimal times: that is, under constant and fully ascertained conditions. This work represents the high water mark of stimulation experiment, and for delicacy of performance, and for its deep analysis of the quality of cortical function it stands alone.

As thus delimited, the motor cortex is said by these observers to be as follows: "the motor field's boundary seems to lie, especially in its lower two-thirds, farther forward than does Campbell's precentral area. The anterior border as determined by faradization, is, however, not a sharp one, and its situation seems to vary somewhat from specimen to specimen. As placed by us, it certainly appears to lie for the most part in the intermediate precentral area of Campbell. Opposite the 'arm area' it lies not far behind the anterior border of the intermediate precentral area, but opposite the 'leg area' it lies very much further behind the anterior limit of intermediate precentral area, although in front of anterior limit of the pure precentral area of Campbell."

For the anthropoid apes, therefore, the motor cortex is the area thus experimentally delimited, and its anatomical substratum is seen to include the whole of Brodmann's area 4 and also the adjacent and posterior part of his area 6.

In man the situation is not different, and in the stimulation studies of Penfield and Boldrey (1937). the most recent of the kind, we find the motor

cortex a well-defined area embracing precisely the regions named by Leyton and Sherrington.[1] These observers state that without any increase in stimulation strength, motor responses of uniform character are found in area 4 (FA) and the adjacent part of area 6 (FB), "*with no particular tendency to follow the cytoarchitectural pattern.*" Even Foerster, whose standardization of experimental conditions appears to have been very imperfect (1931), and whose conclusions differ from those cited in some respects, reports that "stimulation of points of area $6a_\alpha$ (Vogts' nomenclature) produces the same isolated effects that are obtained from stimulation of area 4, and there is the same subdivision into foci for single segments of the limbs, but the threshold is much higher."

Whence, then, the present confusion? Until 1932 the conception of the motor cortex as something purely within the physiological category held the field. It is true, that by many—though not by all—the motor cortex was believed to be anatomically co-extensive with the Betz-cell-bearing area, yet it remained a term with physiological reference. In this year, a new conception was formulated and later expressed thus by Fulton (1933-34): "The motor area is defined histologically as the region of the cortex containing in its fifth layer the large cells of Betz. It should be emphasized that the limits of the motor area are determined by its cellular structure and not by its electrical excitability." Here the physiological properties of the motor cortex are explicitly rejected as irrelevant and an anatomical hypothesis—that is yet to be proved—put in their place as the essential criterion of definition.

Confusion followed fast upon this new definition, and it soon became necessary to restore electrical excitability—though with qualifications—to the definition. Thus, Fulton (1938) says that "the excitability of area 4 in the higher primates and man differs from that of other motor regions of the cortex in the discreteness of its responses," and again (1936) "the functions of the anterior part of the excitable cortex obviously differ from those of the posterior." This anterior part is known as the "premotor" cortex, and its anatomical definition suffers the same confusion as that of the motor cortex. Thus, Bucy (1933) states that the premotor cortex is (*a*) the cortical region immediately anterior to the "classic motor area" and is also (*b*) co-extensive with area 6. Yet, clearly, it cannot be both, for the classic motor area can be no other than that of Leyton and Sherrington which we have seen to include part of area 6; that is, part of what we are now asked to call the premotor cortex.

[1] Penfield and Boldrey also record the presence of some excitable points in the postcentral convolution. Concerned only to determine the topography of the excitable motor cortex, they appear to accept without critical examination the hypothesis that restricts the motor cortex to area 4, and they assume that all motor responses evoked by them from area 6 are really due to activation of area 4. This assumption does not follow from any facts they record.

Finally, we find Fulton and Dusser de Barenne (1933) using the terms " excitable cortex " as synonymous with " motor cortex," and Fulton (1935) stating that " the term ' excitable area ' is applicable to both the motor and premotor regions."

In short, the term " motor cortex " is now used in purely opportunist fashion, and it has ceased to be a term of precision.

A prime necessity in the grammar of science is an unequivocal terminology, each item of which refers to one thing or to one notion, and not to any other thing or notion. Without this, clarity of thought and the interchange of ideas are alike impossible. The motor cortex was originally so named in virtue of certain physiological properties it displays and for no other reason. Indeed, there could be no other valid reason, for in physiology the adjective " motor " has functional and not structural reference.

When we refer to a nerve cell as a " motor " nerve cell we refer to the functions of that cell, its morphology being for the moment indifferent. The same consideration applies to the use of the term " motor cortex " or " motor area." We here refer to function, and function cannot be " defined histologically," but only in terms of function. To specify the anatomical substratum of the motor cortex calls for a statement additional to that defining function. Fulton's new definition confuses the anatomical and physiological categories, and declares irrelevant those very properties from the possession of which the motor cortex derived its name.

It is surely clear, therefore, that we must return to the physiological definition of things and notions physiological. Hence in this review, by the term " motor cortex " we refer to the cortical region delimited physiologically by Leyton and Sherrington in anthropoids, and by Penfield and Boldrey in man. If we now compare the maps of the two former for orang and gorilla and of the latter for man, with Campbell's chart of the distribution of the Betz cells, a distribution regarded as co-extensive with area 4 by all observers prior to Economo and Koskinas, we see that the stimulation maps agree in showing a *uniformly* excitable region of cortex that embraces area 4 (FA) and part of area 6 (FB). In none of these types is the motor cortex coextensive with the Betz-cell-bearing area 4 (fig. 9).

We may now proceed to consider the objections that may be urged against this conception of the motor cortex. These are of two orders; one anatomical, the other physiological. They are as follows:

(1) It has been said that the anterior border of the physiologically delimited motor area is too vague for purposes of definition, and is incapable of anatomical correlation. Forty years ago, this objection might have carried some weight, but it has long since been obsolete now that we have authoritative experimental evidence in anthropoids and man as to

the place and quality of this anterior border. Leyton and Sherrington found that under the influence of "facilitation" the anterior border of their motor cortex can be slightly advanced. This variation is the measure of the vagueness alleged, and it is a variation inherent in the very nature

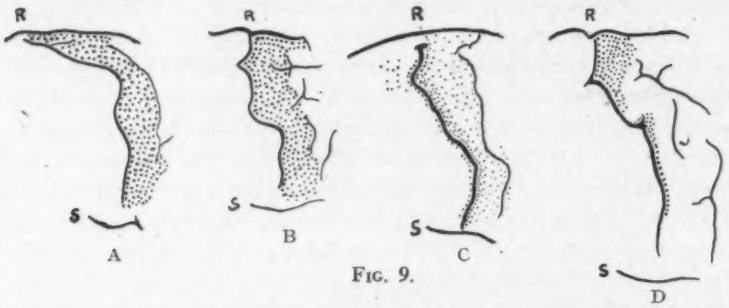

FIG. 9.

FIG. 9, A, B, C.—These diagrams represent in the strippled areas the excitable motor cortex as physiologically delimited. A in the orang, B in the gorilla, C in man. D represents Campbell's chart of the distribution of Betz cells in man and is given for comparison with the extent of the motor cortex. (A and B from Leyton and Sherrington, 1917. C from Penfield and Boldrey. D from Campbell's plate IX.) R is the fissure of Rolando, S the fissure of Sylvius.

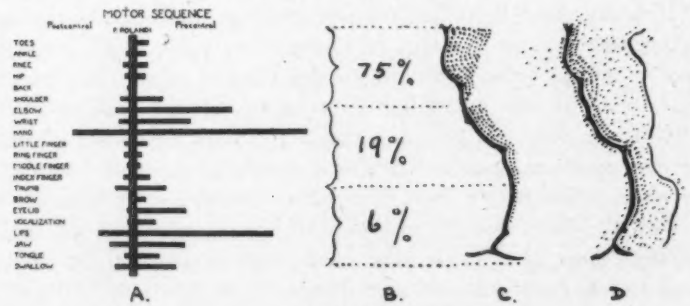

FIG. 10.

FIG. 10.—A diagram showing the relation of the cortical representation of movements in the human cortex (Penfield and Boldrey) with the Betz cell distribution. A. Penfield and Boldrey's motor sequence chart. The list from "toes" to "swallow" indicates the proportional number of points anterior to the fissure of Rolando yielding in the precentral gyrus. The length of the individual horizontal lines to the right indicates the proportional number of points anterior to the fissure of Rolando yielding the movements named. Their length to the left indicates the number of responses evoked from the postcentral gyrus. B gives Lassek's figures for the relative distribution of Betz cells in the three thirds of the Betz cell area. C gives Campbell's diagram of Betz cell distribution. D gives the extent of the motor cortex as delimited by stimulation by Penfield and Boldrey.

of cortical function and is neither incomprehensible nor capricious. Further, so far from providing a contrast with anatomical aspects of the cortex, it accords remarkably with these. As we have seen, there are in fact no "hair-sharp" lines dividing the different cortical areas on cytoarchitectonic grounds, save for a few known exceptions which do not include areas in the frontal lobe. Nothing emerges more clearly from the studies of Economo and Koskinas than the difficulties involved in any precise delimitation of cortical areas, and what Brodmann has to say on the matter in the case of areas 4 and 6 of *cercopithecus* we have already seen. The areas depicted on a cortical map attempt to take into account all the six component layers of the cortex, and, as it were, to strike an average between them; but an ideal cortical map would require a separate sheet for each layer, and, in short, as Economo and Koskinas remark, there is about the border of any cortical area something arbitrary and subjective, dependent upon the particular cell form or lamina we chance to have under consideration. Thus, cytoarchitectonics provide us with nothing more precise than does physiological experiment, for the simple reason that the cerebral cortex is not built as a chessboard. It seems safe to say that neither anatomy nor physiology provide us with any reality corresponding to cortical maps such as those of the Vogts and of Foerster. These constitute a highly artificial 2-dimensional scheme of a 3-dimensional anatomy, and they depict a simplicity in natural objects of which nature knows nothing. There can be, then, no objection on grounds of anatomy to the physiological delimitation of the motor cortex, for just as the anterior limits of the relevant cortical layers in areas 4 and 6 (FA and FB) merge gradually into the changed conditions characteristic of areas lying anterior to them, so does the excitable cortex show a less than "hair-sharp" anterior border. The behaviour of the anterior part of the motor cortex is what its structure would lead us to expect of it.

(2) A physiological objection to the conception of the motor cortex here maintained might be urged if it could be shown that within its boundaries the presence of two distinct physiological mechanisms could be demonstrated. If, for example, it were found that the motor responses elicitable —under standard conditions—by stimulation of area 4 (FA) differ qualitatively from those resulting from stimulation of area 6 (FB) under comparable conditions, it could then be proposed that the Betz-cell-bearing area 4 (FA ~) is a physiological unit and that area 6 is another: then the names "motor" and "premotor" respectively applied to them by Fulton and his co-workers might express a physiological truth. On this point we have

evidence from two main sources, the results of which appear at first sight to be in direct and complete conflict. The first source we find in the studies, already referred to, of Leyton and Sherrington in anthropoids and of Penfield and Boldrey in man. *In these we find no trace of any such dual mechanism within the motor cortex.* As the stimulating electrode passes anteriorly across the cortex of area 4 (FA) on to that of area 6 (FB) the character of the motor responses and the strength of stimulus necessary to evoke them show no change whatever except at the anterior fringe. The responses do not follow "the cytoarchitectural pattern," and we pass from excitable to silent cortex. For man and anthropoids, therefore, the two statements cited from Fulton (p. 434) in respect of these types appear quite without foundation. Stimulation experiments in them have provided no indication of the presence of a "premotor cortex" with functions qualitatively different from those of his "histologically defined" motor cortex, i.e. area 4.

It is only when we turn to the second source, the *cercopithecus* and *macacus* physiology of the Vogts and of Fulton and his co-workers, that evidence purporting to differentiate the reactions of areas 4 and 6 is submitted. In this body of observations we find it stated that as the stimulating electrode passes from area 4 to area 6 the threshold of excitability rises suddenly, and with equal suddenness motor responses of an unequivocally different order appear. For the Vogts, this physiological change has the same "hair-sharp" suddenness that they postulate for cytoarchitectonic borders.

To appreciate fully the basis of this claim it is necessary that we should be quite clear as to what are the qualities of the responses evoked from the motor cortex of Leyton and Sherrington, and the interested reader may be strongly urged to study for himself the relevant chapters in Leyton and Sherrington's classic paper.

They provide a list of over 500 movements observed by them on stimulation of the motor cortex. Each *threshold* stimulus applied for two seconds tends to give a sequence of simple movements, their first, second, third and fourth movements. The first is called the primary movement and it may be followed by one or more secondary movements. If stimulation be strengthened or prolonged, a definite "march" of movements occurs and this may issue in an epileptiform convulsion that persists after cessation of stimulation. Further, movements of all segments of the limbs, proximal as well as distal, and of all parts of the trunk are to be seen, and no movement of the skeletal musculature is unrepresented (save eye movements as primary movements). The nature of the response varies accord-

ing to various named factors, amongst which the most important in our present connection are stimulation strength and duration. As these are raised, the responses become more widespread and therefore complex, and may as we have seen assume the characters of a Jacksonian fit.

Before proceeding to summarize the evidence derived from *macacus* and *cercopithecus*, we may recall that in these studies entire reliance is placed upon the areal chart of C. and O. Vogt. It is clear that conclusions based upon an anatomical foundation so largely uncertain must be taken with reserve.

In contrasting the differences between the motor responses evocable from areas 4 and 6 respectively, Bucy (1933) summarizes area 4 responses as follows: (i) they consist in discrete sustained responses involving small muscle groups, usually distal limb muscles rather than proximal; (ii) if stimulation be strengthened and prolonged the responses are more widespread, may be rhythmic and may issue in epileptiform after-discharge; (iii) with minimal stimuli the cortex anterior to a line from 5 to 7 mm. in front of and parallel with the fissure of Rolando is inexcitable. This line is said to correspond accurately with Vogts' line of division between areas 4 and 6. To demonstrate excitability in area 6 it is necessary to raise the strength of stimulation. When this is done motor responses are obtainable from the posterior part of area 6. With threshold stimuli these resemble the responses obtained from area 4, though the localization of the movements is said to be "less discrete." With stronger stimuli "an entirely different type of movement" is obtained, consisting of rhythmic and progressive movements. The last named are obtained with maximal stimuli and are so-called because they show after-discharge. If the cortex along the line assumed from the map to separate areas 4 and 6 be incised, no responses are any longer obtained from area 6 to near-threshold stimuli, but with maximal stimuli diminished rhythmic and progressive movements may still be obtained.

From these observations the following conclusions have been drawn: (i) The premotor cortex represents a motor mechanism with functions other than those of area 4; (ii) the disappearance of simple segmental movements on stimulation of area 6, when a cut separates it from area 4, shows that the impulses engendered in the former normally travel backwards through the cortex to the giant cells of Betz in area 4, and exciting these cells give rise to motor impulses which descend the pyramidal tract; (iii) the persistence of rhythmic and progressive movements when a cut separates areas 4 and 6 shows that the latter has its own long projection

tract distinct from the pyramidal tract; but (iv) the diminution in these movements in these circumstances show that some of the impulses responsible must also travel back to the Betz cells and descend thence by the pyramidal tract.

Various comments occur to the reader of this interpretation. It is difficult to ascertain in what consists this alleged *qualitative* difference between the reactions evocable from area 4 and some of those obtained from area 6. The latter do not seem to differ essentially from those we find when area 4 is *maximally* stimulated: namely widespread movements with after-discharge that may issue in an epileptiform convulsion. On this point, also, Horsley in the lecture already cited has a pertinent comment to make: "it should not, in my opinion, be assumed that the effect of a minimal stimulus, evoking, as it often does, but a single movement of a single segment of a limb, is a criterion of all that is represented —that is within that portion of the cortex cerebri."

It seems that as the anterior limits of the motor cortex are reached, the threshold of excitability rises, though it may be lowered even here by "facilitation," and at this previously inexcitable fringe, increased stimulation strength and duration will serve to evoke the simple segmental movements described by Bucy (and earlier described by C. and O. Vogt). With still stronger stimuli more extensive and longer-lasting movements appear and show after-discharge, and finally large fields of the musculature can be thrown into action. That some of this motor activity may be due to spread of current to posteriorly-lying cortex seems likely from the described effects of cutting a trench between areas 4 and 6. We have indeed seen in Foerster's cortical stimulation studies in man (1931) what very wide regions of the cerebral cortex can be made to yield movements on maximal stimulation, but to say that all the movements obtained in these circumstances indicate a normal motor function of the cortical regions stimulated would not be justified, and indeed, the more careful exploration of the cortex by Penfield and Boldrey has shown that Foerster's findings cannot be accepted. In this supposed selective excitability of the premotor cortex with its qualitatively distinct motor responses, therefore, it seems far more likely that we are seeing the results of the maximal stimulation of the *relatively* inexcitable anterior fringe of the motor cortex that lies in area 6 (FB), together with effects due to spread of current through the cortex to area 4. *All that can be elicited from this supposed premotor cortex can also be elicited from the rest of the motor cortex if this be sufficiently strongly stimulated.* It is interesting to note that the barbiturate anæsthetics are said totally to destroy the excitability

of the premotor cortex, light ether anæsthesia (used by Leyton and Sherrington and by Bucy) is less depressant, but Penfield and Boldrey's stimulations were carried out in man under local anæsthesia, so that no question of any depression of cortical activity could arise. Yet under these favourable circumstances, these observers detected no trace of a physiologically distinct premotor mechanism.

Therefore, cortical stimulation experiments may be said to provide no satisfactory evidence of any division of the physiologically delimited motor cortex into two separable components. *The motor cortex as far as its activities can be displayed by this method is one and indivisible.* The cortex lying anterior to it appears electrically inexcitable.

Further evidence of the qualitative differences in function between the cortex of area 4 and that of area 6 is said to be provided by isolated ablations of these two areas, but the conflict of evidence here is so considerable that no conclusions can be drawn from these experiments. Thus area 4 ablations are said to provide hemiparesis, most marked in the distal limb segments, transient depression of tendon-jerks and transient flaccidity. In some experiments later increase in tendon-jerks and some hypertonus are recorded. Area 6 ablations are in some accounts said to produce marked spasticity, hemiparesis and apraxia (Fulton, 1935), but in other accounts (Fulton, Jacobsen and Kennard, 1932) these ablations were said not to lead to pronounced hypertonia. Repeating these experiments, Denny Brown and Botterell (1936) found after area 4 ablations in *macacus* the type of hemiplegia familiar to clinicians, flaccid at first and then developing increased tendon-jerks and hypertonus of the distal limb segments, while area 6 ablations yielded a uniform hypertonus resembling that known to clinicians as "extrapyramidal rigidity." Stimulation of area 6 after ablation of area 4 did not yield the complex movements described by Bucy, but, in some experiments, inhibition of the resting tonic posture of the limbs.

It is clear that we have not yet reached finality of observation in this field of *macacus* cortical physiology, and it is interesting that Denny Brown and Botterell found that the Betz cell-bearing area in their animals did not correspond to the cortical map of C. and O. Vogt, but to that of Brodmann.

Therefore, the apparent discrepancy beween the results of experiment in the anthropoid apes (Leyton and Sherrington) and those in the lower apes, resolves itself by the inconclusive nature of the latter which provide no clear evidence of such a dual motor cortex mechanism as that postulated by Fulton and his collaborators.

There is therefore no real discrepancy between the results of human and anthropoid cortical experimental studies, on the one hand, and those of *macacus* and *cercopithecus* physiology on the other that cannot be accounted for in terms of the misinterpretation of some, and of the inconclusive nature of other, experiments in the latter category.

Brief mention may be made of the fact that comparable cortical stimulation and ablation experiments have been made on the cat and dog, with no general agreement as to either the results or their interpretation. These are referred to by Woolsey (1933) whose observations were made on dogs. He found the excitable cortex of wider extent than the Betz-cell-bearing area, and yielding a uniformity of motor response to stimulation that gave no evidence of two separate components of different function. Ablation of the excitable area gave spastic hemiparesis, but ablations of cortex anterior to this area produced neither spasticity nor paralysis of movement.

Reference has been made to the possibility that cortical functions may have to be considered in terms of cortical layers. The notion of a cortical laminar pathology is no new one, and the relevant facts are briefly described by Economo and Koskinas. That there should be a laminar pathology presupposes a laminar physiology. So far only one approach to the exploration of this has been made, namely by Dusser de Barenne and his co-workers (1934, 1936, 1941). They found that thermo-coagulation of the entire depth of the cortex in the precentral convolution produced a contralateral paralysis and an abolition of cortical electrical potentials (electro-corticogram), but if layers V and VI are left intact, only very transient paralytic symptoms and no change in cortical potentials follow. As far as they go, these experiments seem to indicate that layer V is of primary importance in the motor functions of this cortical region, but they do not serve to differentiate between the different cells of layer V. They do not prove, as has been claimed for them by Fulton (1936), that the motor functions of area 4 reside in the giant cells of Betz.

Conclusions.

Physiological experiment, therefore, despite recent claims to the contrary, does not confirm that the motor cortex can be divided into two separable components of distinct and different function. The observations of Leyton and Sherrington, of Penfield and Boldrey reveal nothing that even suggests the possibility of such a division. From their experiments the motor cortex emerges as one and indivisible. It embraces the whole of area 4 (FA) and the adjacent posterior part of area 6 (FB). It seems probable that the hypothesis of a separate cortical motor mechanism

in the region of the anterior border of the motor cortex arises from two causes: (i) the view that the Betz cell is a specific cell, and (ii) a misinterpretation of the results of maximal stimulation of the relatively inexcitable fringe of the motor cortex. The widespread movements seen in the circumstances have been compared with the small segmental movements resulting from minimal stimuli applied to the low-threshold part of the motor cortex, and it has been overlooked that maximal stimulation of this region also gives rise to widespread movements and sequences of movements. By comparing two sets of phenomena that are not strictly comparable, the erroneous conclusion is reached that qualitative differences obtain between them, and thus the preconceived notion that the Betz cell is a specific entity obtains a fallacious confirmation.

In Leyton and Sherrington's and in Penfield and Boldrey's observations this error was avoided and thus no evidence of a dual cortical mechanism in areas 4 and 6 was obtained.

It appears, also, that the motor cortex is not co-extensive with a cortical "area," a result that need not surprise us when we realize the true nature of cortical areas. It seems that the true correlation of function and structure here is between motor functions and the large pyramidal cells of layer V in areas FA and FB. In an earlier paper (1935) the present writer submitted that the motor cortex is not co-extensive with area 4, and drew from Foerster (1936) the protest that "the opinion has recently been expressed that the different cyto- and myeloarchitectonic structure of these areas were merely anatomical details without physiological significance," but it is now clear that he was correlating function, not with structure, but with maps, and we see that applied cytoarchitectonics are wandering from the realities of anatomy. Economo and Koskinas have clearly pointed out the limitations and the nature of the areal map, but for C. and O. Vogt, as for Foerster, their cortical maps are precise guides of universal validity for every component of every cortical field in every individual brain.

These maps do not possess a factual accuracy of this high order, and it is unthinkable that they should do so. They cannot be treated as though they were mariner's charts which record the precise and unchanging form and extent of individual concrete structures.. Yet this is how they are being increasingly treated, and applied cytoarchitectonics are thus ceasing to provide the basis of a scientific correlaton of function and structure. Perhaps the superlative example of this is Foerster's map of cortical areas in man, which is no more than a *cercopithecus* map of uncertain accuracy redrawn upon a diagram of the human brain. It is

not the record of any human cytological studies, and the arbitrary process of its production is spoken of as "homologizing the map for man." It would be difficult to conceive of a chart more remote from the realities of the structures it purports to represent.

IV.—THE BETZ CELLS, THE MOTOR CORTEX AND THE ORIGIN OF THE PYRAMIDAL TRACT.

"Ebenso wie Cajal möchten wir ebenfalls annehmen, dass die grossen Pyramidenzellen und Riesenzellen der IIIc und V neben den Betzschen Kolossalzellen auch als Ursprungszellen der Willkürbewegungen und der Pyramidenbahn sind und das diese verschiedene Zellen also nicht anderes als durch ihre Grösse unterschiedene Individuen ein und derselben Zellart sind, deren Zellgrösse jedoch gewissermassen in umgekehrten Verhältnis zur Feinheit und Individualisierung der ausgelösten Bewegung steht."—Economo und Koskinas. "Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen," 1925, p. 290.

The conclusions that have been submitted from the available facts concerning the anatomical status of the Betz cell, in relation to other pyramidal cells and to the motor cortex, have prepared us for the probability that the pyramidal tract,[1] indeed, the entire category of upper motor neurones as this term is commonly understood, arises from the large pyramidal cells and the simple giant cells of cortical layer V within area FA and the adjacent part of FB as well as from the giant cells of Betz. This is explicitly the view taken by Economo and Koskinas, and they portray on the surface of the cerebral cortex what they believe to be the cortical region corresponding to the field of origin of the fibres. Their diagram is here reproduced.

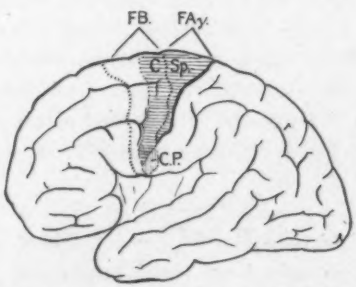

Fig. 11.—Economo and Koskinas' fig. 87 (p. 185) representing the presumed cortical field of origin of the corticospinal (pyramidal) and cortico-pontine fibres.

[1]The pyramidal tract comprises all the corticospinal fibres, and these fibres alone. As far as is known these all traverse the medullary pyramid. Above this level they are not wholly segregated, and it is possible that in the spinal cord this may also be true of them, but in the medullary pyramid nothing is known of any admixture of other than corticospinal fibres.

In citing authorities, however, we must beware of laying too much emphasis upon opinions that do not arise directly and necessarily from their observations, and it may be asked whether cytoarchitectonic studies can provide a conclusive answer to the question of the exact origin of the pyramidal tract. This at least we may say, that these studies show the close relationship between the three categories of pyramidal cells named above, and provide no ground for an exclusive attribution to the Betz cells of the origin of the pyramidal tract. The distribution of the Betz cells of itself affords strong evidence against such an attribution, for no less than 75 per cent. of them are found in the " leg and trunk areas " of the motor cortex, the extensive representation of the upper limb movement contains only 19 per cent., and the movements of the head, neck and face regions only 6 per cent. (Lassek, 1940), (see fig. 10).

It is therefore incredible that the giant cells of Betz should give rise to all the long projection fibres serving the motor cortex and comprising the pyramidal tract and the shorter path to the brain-stem motor nuclei. Even if we consider the cortical representation of upper limb movements alone, we know that the region concerned contains a relatively small proportion of the Betz cells, but a very large number of simple giant and of ordinary large pyramidal cells, and we cannot escape the inference that the axones of the two latter groups must play a part in the motor functions of this region and contribute to its corticospinal projection. If, as has been stated, the ratio of the Betz cells to pyramidal fibres is as 1 : 40, how much greater is the discrepancy of numbers when we include the projection fibres to the brain-stem nuclei.

The recent fibre analyses of the pyramidal tract (Häggqvist, 1937; Lassek and Rasmussen, 1939; Lassek, 1942, *a*) seem to confirm the inadequacy of the Betz cells, numerically, to provide all the axones of the pyramidal tract even when due allowance is made for the difficulty in the precise identification of the Betz cell, and even if we double the largest current estimate and make the total 60,000 Betz cells. Lassek and Weil's (1929) original count gave 250,000 pyramidal fibres in the cervical pyramidal tract, but later counts with more refined staining methods have given considerably larger figures. Lassek and Rasmussen (1939) give one million in man, and in a more recent count still Lassek (1942, *a*) finds in two young adults approximately 750,000 fibres. Still other interesting details have emerged from these studies. Thus, Häggqvist finds that the largest pyramidal fibres arise in the " leg area ": that is, where the Betz cells are largest, the smallest fibres arising at the other extremity of the motor cortex

where the Betz cells are smallest and fewest. He gives the range of fibre diameters as from 3μ to 21μ, five-sixths of the total being of the smallest calibre and these he concludes to arise outside area 4. Lassek and Rasmussen, and Lassek (loc. cit.) find the pyramidal tract mainly composed of fine calibre fibres, only 4 per cent. having a diameter of more than 10μ. Lassek classifies these fibres into four groups: small fibres of from 1μ to 4μ, medium fibres of from 5μ to 10μ, and large fibres of from 11μ to 20μ. Of the total, 89·57 per cent. are small, 8·7 per cent. medium and only 1·73 per cent. large. Over half the total were only 1μ in diameter. Further, of the total, no less than 39 per cent. were non-medullated. Ranson (1913) and Wheelis and McKibben (1932) had previously reported the presence of non-medullated fibres in the pyramidal tract. The recognition of these non-medullated fibres has made possible more accurate fibre counts than heretofore.

From these findings certain inferences may be made. The pyramidal tract must be a slowly conducting path, since conduction rate increases with fibre diameter, as indicated in the writer's earlier review on cutaneous sensibility (1942). Therefore the pyramidal tract cannot be the "fast-train" pathway to the lower motor neurone postulated by Foerster (1931). Moreover, it seems unlikely that the giant cells of Betz can be responsible for the vast number of tiny non-medullated fibres of which the pyramidal tract is seen to be partly composed. It is probable that they provide the small percentage of large fibres.

There is still another method of approach to the problem. If all the pyramidal fibres arise from Betz cells in area 4, ablation of this area should produce total degeneration of the pyramidal tract. Yet it has long been known that this does not ensue. Monakow (1915) pointed out that it required total destruction of the hemisphere to cause total loss of pyramidal fibres, and Schröder (1914) reported that loss of all Betz cells left the pyramidal tract apparently intact. Lassek (1942, *c*) performed cortical ablations in six monkeys, allowed periods of from nine to eighteen weeks for degeneration to ensue before destroying the animals. After ablation of area 4, from 60 to 75 per cent. of pyramidal fibres remained intact, and even more extensive ablations left 50 per cent. of the fibres intact. Häggqvist (1937) found that four-fifths of the pyramidal fibres survived motor cortex ablation, the missing one-fifth being the largest fibres.

We are thus brought back to a consideration of the value of the method of reactionary chromatolysis, originally used by Holmes and Page May, and the original basis of the hypothesis that Betz cells alone give rise to pyramidal fibres.

It may be stated at once that we yet lack any final conclusive and positive demonstration that division of the axone does not invariably lead to retrograde degeneration of the cell of origin, but there is strong evidence that it does not. Thus, Tower (1940) found after division of the medullary pyramid that the pyramidal fibres were intact at pontine level above the section, while Davison (1937), in cases of thrombosis of the anterior spinal artery in man at medullary level, found that pyramidal fibre degeneration, proximal to the complete demyelinization of the pyramid at the lesion, did not even reach the pontine level where the fibres were all intact. If then, both in monkey and in man, division of the pyramid does not cause degeneration of the fibres proximally, it would be remarkable if all the cells of origin of the fibres underwent reactionary chromatolysis. Further, Levin and Bradford's finding that 20 per cent. of the Betz cells remain intact after division of the cervical pyramidal tract is significant and suggests that even these large cells do not all undergo retrograde change.

Lassek's most recent study (1942, *d*) still leaves the question unanswered. He divided the pyramidal tract in the first cervical segment in the monkey, and found that while the proximal parts of the severed fibres showed no degeneration, yet the Betz cells of area 4 did undergo retrograde degeneration and disappeared. He supposes that what has happened to them is that they have not fully degenerated, but that they have merely lost their Nissl substance and have shrunk so as to become undistinguishable from the numerous surrounding large pyramidal cells. These having no Nissl granules to lose do not change their appearance, and thus a fallacious impression is gained from the study of Nissl sections. Such a view scarcely accords with the finding of Holmes and Page May that all stages of degeneration can be seen in the Betz cells after pyramidal section, together with evidence of neuronophagia, and it seems, therefore, that the observations of these pioneer workers still stand uncontroverted. Nevertheless, the weight of evidence from many sources outweighs—it is reasonable to submit—any inferences we may draw from the method of retrograde degeneration. There are some three quarters of a million pyramidal fibres to be accounted for, many of them fine and unmedullated, and 30,000 Betz cells cannot account for them. Possibly, quantitative studies of Nissl sections: i.e. counts of the pyramidal cells in layer V of the relevant region before and after pyramidal section might throw more light on the matter. Possibly, too, we are asking of the Nissl staining method more than it is capable of telling us.

In conclusion, therefore, both anatomical and physiological evidence

points to the conclusion that in layer V (possibly also in layer IIIc) of the cerebral cortex we have a group of large pyramidal cells which include the giant cells of Betz, the simple giant cells and the large ordinary pyramidal cells, and that the axones of this group subserve the function of a projection system for the motor cortex. The cortical region in which these cells are found, and therefore the region from which this pyramidal projection system arises, include the whole of area 4 (FA) and the posterior adjacent part of area 6 (FB). These cells and their axones constitute an anatomical unit performing a unitary function. Nevertheless, in spite of the compelling facts of anatomy on which these conclusions are based, we still find wide expression of the view that the Betz cell is the sole cell of origin of the pyramidal tract, and that all corticospinal fibres arising in the Betz-cell-free part of area 4 (FA) and in area 6 (FB) are not pyramidal fibres, but belong to a special extrapyramidal tract subserving an anatomically and physiologically distinct "premotor" cortex. When we seek the basis for this proposed division of corticospinal fibres, we find that it does not necessarily arise from any recorded facts of observation, but from the hypothesis which runs as a repetitive theme through so much recent literature on the subject that the Betz cell is a specific morphological and physiological entity in a category by itself. Into what difficulties this assumption leads us becomes increasingly apparent as we follow it to its logical conclusion.

These difficulties began to appear when it was found that corticospinal fibres arise from area 6 in *macacus*. Thus, Kennard (1935) noted Marchi degenerations in the pyramidal tracts after ablations of area 6, while Hoff and Hoff (1934) and Hoff (1935) detected degeneration of the synaptic terminals of corticospinal fibres in the grey matter of the spinal cord after ablations of the same area, as well as after ablation of area 4 alone.

Kennard found that Marchi degeneration in the crossed and uncrossed (ventral and lateral) pyramidal tracts after ablation of area 6 were to be found uniformly scattered thoughout these tracts. They did not form a special tract, but mingled with the pyramidal fibres. Her only reason for regarding these degenerated fibres as extrapyramidal was that they arose in area 6. They were therefore excluded *ex hypothesi* from being pyramidal fibres, and for no scientific reason.

In this way the "histologically defined motor cortex" of Fulton became endowed with its own pyramidal projection system arising in area 4, and the premotor cortex with a separate projection system arising in area 6. Both systems "followed the anatomic course of the true pyramidal path-

ways," but they were different merely because they arose in different cortical areas. After ablation of area 4 the numbers of these degenerated fibres in the pyramidal tracts was very much greater than after area 6 ablations.

Hoff and Hoff approached the problem in a somewhat different way. The results of Marchi degeneration studied after division of the corticospinal tract having given inconclusive results in the hands of very numerous observers, they took advantage of the fact that after such division the synaptic terminals of these fibres ("boutons terminaux," "Endfüsse") degenerate rapidly. Within a few days they lose their normal loop-like appearance and become easily distinguishable granular masses lying round cells in the grey matter of the spinal cord.

These degenerated terminals are to be seen at the base of the dorsal horns of the grey matter and also more ventrally in the mid region of the grey matter and in the basal parts of the ventral horns.

These abnormal appearances were found to follow (*a*) ablation of area 4; (*b*) ablation of area 6; and (*c*) the cutting of an incision between areas 4 and 6. In their first paper Hoff and Hoff concluded that areas 4 and 6 both contribute to the pyramidal tract, and from the fact that a trench between these areas also leads to terminal degeneration they conclude that some of the projection fibres from area 6 run backwards into area 4 before turning deeply into the white matter. In a second paper, however, Hoff (1935) somewhat added to these conclusions by expressing the view that two groups of projections fibres are in question, a group from area 4 and another group from area 6. Thus the facts are forced into line with the hypothesis that there are pyramidal and extrapyramidal corticospinal projection tracts.

Yet the facts of observation are the same in both series of experiments, and it is not clear that any conclusion can be drawn from the second that is not inherent in the first. Fulton, however, suggests (1938) that there are differences in the distribution of the degenerated terminals within the grey matter according to whether the fibres bearing the terminals arise in area 4 or in area 6. There is nothing in the charts given by Hoff in either of the two relevant papers to bear out this contention. Therefore, these observations prove no more than that corticospinal fibres arising with area 4 and the adjacent posterior part of area 6 run together in the pyramidal tract and end in the grey matter of the spinal cord. Of the existence of two anatomically and physiologically distinct projection systems they provide no evidence.

There is, on the other hand, some experimental evidence to show that the fibres arising from the relevant cells of the motor cortex and travelling in the pyramid of the medulla and pyramidal tracts of the spinal cord are all of one physiological category and do not subserve two distinct cortical motor mechanisms of different function. Tower (1940) has found that section of the pyramid in the medulla of the monkey produces a hemiplegia in which the " positive " element, so characteristic of residual hemiplegia in the human subject, is absent: that is, there is no spasticity. This finding cannot perhaps yet be regarded as wholly confirmed, because Marshall (1934, 1935) finds in the cat that there is some evidence of extensor hypertonus, but the absence of hypertonus appears to have been complete in Tower's monkeys. Now, it has been claimed that area 6 ablations of the cortex produce a notable contralateral hypertonus of the limb musculature, and even if we do not accept that hypertonus is wholly absent after area 4 ablations, it does appear that ablations of the anterior part of the physiologically delimited motor cortex where this lies in area 6 are associated with a definitely greater degree of hypertonus than in the case of ablations restricted to the posterior part of the motor cortex. How this is to be accounted for will be discussed subsequently, but it may here be said that Fulton and his co-workers interpret the development of this hypertonus as due to the interruption of impulses normally arising in the cells of premotor cortex and acting upon lower lying motor mechanisms. On this hypothesis, the residual spastic hemiplegia is the result of two factors: (i) loss of voluntary movements directly due to the destruction of the pyramidal tract arising in the Betz cells of area 4, and (ii) increase of tonic reflex mechanism activity due to its release from the control of the premotor cortex when the extrapyramidal projection tract from this cortex (i.e. area 6) is destroyed by the capsular lesion that interrupts both pyramidal and extrapyramidal tracts. The view that the cerebral lesion underlying a spastic residual hemiplegia might upon analysis be found to have two components: namely, a negative lesion of the corticospinal tract, and also one of another descending path from the cortex (though not necessarily a corticospinal path) was expressed a number of years ago by the present writer (1919), and this is in fact the view adopted by Fulton and his co-workers, with the difference that for them this second descending path is the extrapyramidal corticospinal path from the premotor cortex of area 6.

But it is this difference; this identification of the second path with the projection system of a supposed premotor cortical mechanism, that creates

an insuperable difficulty, for if this system runs with the pyramidal path through the medulla and also in the pyramidal tracts of the cord, it also must be interrupted by a section of the medullary pyramid and therefore, *ex hypothesi,* section of the pyramid should produce the same spastic hemiplegia as results from the ordinary lesion in the internal capsule that underlies the familiar human hemiplegia. But, according to Tower, this is not what happens. The hemiplegia thus produced is flaccid, and therefore either there has been no section of an extrapyramidal path from the premotor cortex, or, if there has been, then this path cannot have the specific functions attributed to it in Fulton's hypothesis.

This vital flaw in the hypothesis has not escaped the notice of Ranson (1936) who in a discussion on the projection tracts of areas 4 and 6 pointed out that according to some current views of the premotor cortex, section of the pyramid should produce spastic hemiplegia.

A final conclusion on this point must await further investigation of the effects of isolated section of the pyramidal tract, though the results of Tower's experiments appear sufficiently conclusive, and, if accepted, entirely rule out the view that the pyramid and pyramidal tract contains fibres of two separate corticospinal projection systems, motor and premotor, each having distinct and quite different functions.

It yet remains possible, however, that the spastic residual hemiplegia is the fruit of a double lesion, but that the path the interruption of which adds the component of spasticity to the hemiplegia, although cortical in origin, does not arise exclusively in the cells within area 6, and that it is a short path going to subcortical centres and not to the spinal cord. The point will be referred to subsequently.

V.—SOME CONSIDERATIONS ON THE FUNCTIONS OF THE MOTOR CORTEX.

"In the course of our work we have frequently had occasion to notice the unscientific process of multiplying existences beyond what are really needful to describe phenomena. The canon of inference which forbids this is one of the most important in the whole field of logical thought. It has been very concisely expressed by William of Occam in the maxim: Entia non sunt multiplicanda præter necessitatem. . . . Sir William Hamilton expresses Occam's canon in the more complete and adequate form: Neither more, nor more onerous, causes are to be assumed than are necessary to account for the phenomena."—KARL PEARSON. "The Grammar of Science," Part 1, Third Edition, 1911.

In our consideration of available facts of observation as to the nature of the giant cell of Betz, the origin of the pyramidal tract and the anatomical substratum of the motor cortex, we have seen that a large body of hypo-

thesis has been formulated from the interpretation, and upon occasion from the probable misinterpretation, of these facts. On the one hand we have the view advanced by Leyton and Sherrington which, containing no elements in conflict with the facts of anatomy, and no superfluous hypotheses, presents the motor cortex as co-extensive with the excitable frontal cortex and as a single indivisible mechanism physiologically considered. For an account of its functions viewed as a whole the reader must be referred to the original paper, but here we need only point out that the authors emphasize the highly co-ordinated nature of even the simplest and most restricted movement evoked by cortical stimulation, and the facility with which the motor cortex welds these fragments into complex movement combinations and sequences that are "eloquent of purpose." Nothing was found by these observers calling for any subdivision of the excitable cortex into separable anatomical or physiological components, nor has the later work of Penfield and Boldrey on the human cortex yielded any new fact necessitating any modification of the observations or deductions of Leyton and Sherrington.

On the other hand, we have another view on the matter, that associated with the name of Fulton and his collaborators, which from observations upon the lower apes has postulated a highly complex dual organization of the excitable cortex.

More than this, it rejects one of the most firmly based conclusions of the work of Leyton and Sherrington, and that of Hughlings Jackson in clinical neurology: namely, the doctrine of the cortical representation of movements, and postulates that in the "histologically defined" motor cortex: i.e. area 4, it is not movements but individual muscles that are represented. Thus, Fulton states:

"There has been a good deal of academic discussion as to whether individual muscles are represented in the motor cortex, or merely movements. Sherrington once said[1] that the central nervous system 'functions' in terms of movement rather than in terms of muscles, and the great neurologist, Hughlings Jackson, argued from his studies of epileptic seizures, that movements rather than single muscles find representation in the cerebral cortex: from this he argued that specific movements are impaired following cortical lesions, rather than specific muscles. Movements, i.e. highly organized patterns of response, are indeed represented in the cortex as we shall see later, but in so far as the motor area is concerned, I would urge that the representation is of muscles rather than of movements. By means of this final common pathway from the cerebral mantle, over which travel highly organized integrations, individual muscles may be thrown into action in appropriate combination and

[1] Chapter VIII of Sherrington's "Integrative Action of the Nervous System" is devoted to the reactions elicitable from the motor cortex, and presents in detail the evidence upon which their status as coordinated movements is accepted.

sequence. By discrete stimulation of Betz cells single muscles, indeed small parts of a given muscle, can be thrown into activity. From this fact I regard it as proper to speak of a muscle having representation in the motor area, movements having representation in the larger cerebral organization of the frontal lobe."—(Hektoen Lecture, 1936).

This is strange reading when we remember that reciprocal innervation obtains in every movement elicited by cortical stimulation and that in man the paralysis of a muscle as such is never seen in cerebral lesions, but only paralysis of movements. It would not be germane to our purpose to cite this lengthy and obscure passage were it not that it provides an illustration of the conclusions to which Fulton's hypothesis of a dual motor cortex inevitably leads him, and it is now the moment to view this hypothesis as a whole. Primarily based upon the assumptions that the giant cell of Betz is a specific cell with exclusive functions as the essential element in a " histologically defined " motor cortex, and that the pyramidal tract is composed solely of axones of these cells, it has to account for the fact that the cerebral cortex immediately anterior to the Betz cell area is also electrically excitable. The threshold of excitability of this region of cortex is high at its anterior limits, but, when a threshold is obtainable here, stimulation at this strength yields simple restricted movements not distinguishable from those obtained by threshold stimulation of the Betz cell area. Yet to strong stimuli it yields widespread movement sequences. These are then contrasted with the simple segmental movements elicited from the posterior part of the motor cortex by *threshold* stimuli, the fact that maximal stimuli applied here also yield widespread movement combinations and sequences with after-discharge being ignored. Thus, by comparing phenomena that are not strictly comparable and neglecting to compare those that are comparable, the conclusion is reached that there is a *qualitative* difference of function between the anterior and the posterior parts of the motor cortex. In this way, it becomes possible to postulate the existence of two cortical motor mechanisms within the excitable region, a " histologically defined " motor cortex in area 4, and a " premotor cortex " in area 6. It now becomes necessary to provide each with its projection system. This is achieved by a fresh hypothesis; namely, that all corticospinal fibres arising in area 4 are to be called pyramidal, while all those that arise in area 6 are to be called the extrapyramidal projection system of the premotor cortex. The functions of the two systems thus brought into being are different, destruction of the one—area 4 and the pyramidal tract—produces simple hemiplegia without hypertonus, destruction of area 6 and its projection system leading to hypertonus.

So far we are dealing only with a multiplication of hypotheses, each one arising, not so much out of the facts as out of its immediate predecessor in the chain, but at this juncture a direct conflict occurs, for *ex hypothesi,* section of the pyramid in the medulla must interrupt both of these projection tracts and should thus produce hemiplegia with spasticity. Yet, according to Tower's experiments, only a flaccid hemiplegia results from this lesion. No subsidiary hypothesis has yet been formulated to remove this difficulty.

The final link in the chain of hypotheses is provided by the last assumption that in the cortex of area 4 individual muscles are represented, while in area 6 movements are represented. Thus the contrast between the two mechanisms is brought to its logical conclusion.

In the final form the hypothesis takes we have a plethora of " more, and more onerous, causes " than are required to deal with the phenomena, with the addition of a direct conflict of hypothesis with phenomenon in the matter of the two projection tracts. It is impossible not to be reminded by this situation of Head's theory of the constitution of the afferent nervous system, in which the initial postulation of two unnecessary and unverified anatomical arrangements: the epicritic and protopathic systems, led to the inevitable formulation of a series of subsidiary hypotheses; each called into being *ad hoc* to meet the difficulties created by the initial assumptions, yet failing in the end to provide a coherent hypothesis that generalized the facts of observation.

We may conclude, therefore, that the inferences drawn by Leyton and Sherrington as to the functions and constitution of the motor cortex alone provide a scientific generalization of the relevant phenomena: that is, the simplest possible satisfactory generalization. These inferences and those of Hughlings Jackson must still command our assent, which makes it impossible for us to accept the new and redundant hypotheses of Fulton and his collaborators, with which indeed they are in conflict. In short, the facts of observation do not require and therefore do not justify the postulation of the two mechanisms " histologically defined motor " and " premotor " of Fulton's hypothesis.

There remains for brief consideration one other feature of cortical motor function for which the clinical neurologist yet awaits a satisfactory elucidation. Familiar with the clinical picture of residual spastic hemiplegia, as this results from a cerebral vascular lesion, he requires a conception of cortical motor function that will account not only for the loss of movement that he observes, but also for the characteristic hypertonus and

other positive phenomena in the clinical picture. Jackson has formulated the general principles that govern the appearance of " release " symptoms, but whether this release is—like the loss of movement—a result of loss of upper motor neurone function, or requires the loss of function in some other neurone system remains problematical. We have seen how Fulton has attempted to provide the answer to this problem, and with what lack of success. The occasional occurrence of hemiplegia without concomitant positive symptoms is on record, sometimes with cortical, sometimes with more deeply seated cerebral lesions. Thus Davison and Bieber (1934) have described a series of cases of hemiplegia from vascular lesion, namely, middle cerebral artery thrombosis, in which despite extensive damage to the " premotor " area (area 6) the hemiplegias remained flaccid throughout life. So far, then, human material has not provided an answer to this question. Many years ago (1919) the present writer was led to suggest that " from clinical and experimental sources come several indications, as yet imperfectly understood, that a pure cortical lesion of the pyramidal system often does not produce spasticity as an accompaniment of the loss of power. They suggest the possibility that in the cerebral lesion underlying, for example, a typical spastic residual hemiplegia, analysis may ultimately reveal a second component. That is, that in addition to a negative lesion of the corticospinal path, interruption of another descending path may be concerned in the production of spasticity. Such a path need not be cerebrospinal."

It may be worth while, therefore, to consider the relevant facts of anatomical and experimental observation to see whether they throw any light upon the dual symptomatology of what is known to the clinician as the upper motor neurone type of paralysis, of which hemiplegia with spasticity provides the most familiar example.

Let us attempt the task on the basis of the laminar physiology of the motor cortex already referred to. We have seen that in layer V of the motor cortex we have a large group of pyramidal cells, all of one " Zellart " and including the giant cells of Betz, the simple giant and the large pyramidal cells. This layer, or field, of cells coincides with the limits of the motor cortex and with the field of origin of the pyramidal tract. It is not unreasonable to assume that this group of cells and their axones make up the anatomical basis of a unit of physiological function, the motor cortex. Dusser de Barenne's thermo-coagulation experiments, already referred to, afford some measure of support to this view in that—as far as they go—they seem to indicate that the cells of layer III play no significant role in this unit of function.

Let us also consider the possibility that the field of simple giant cells and of large pyramidal cells of layer III in area FA and the greater part—if not the whole—of Area FB, constitutes the anatomical basis of another physiological unit. The extent of this unit, measured in terms of cortical areas, is greater than that of the relevant cells of layer V, for as we have seen the large pyramidal cells of layer III reach in area FB dimensions only second to those of the giant cells of Betz. We have no information whatever as to the nature of the projection system arising from this group of cells, but *no evidence that it is corticospinal.* We do know, however, that there are short projection tracts arising in areas 4 and 6 in monkeys. These include a precentro-pontine tract, cortico-rubral and cortico-nigral tracts (Levin, 1936) and corticotectal tracts (Beevor and Horsley, 1902).

It is possible that one or more of these short tracts may constitute the projection system of our group of cells in layer III of area FA and FB. These cells and their axones may thus constitute the system, a negative lesion of which permits the development of the positive symptoms of hemiplegia. The extension of this field of cells well into area FB, in which its focus may well lie, may account for the more marked degree of hypertonus that ensues when ablations encroach upon the region immediately anterior to the motor cortex. Thus we should have two physiological units, overlapping when considered in terms of cortical areas, but not coextensive: units the presence of which might not only account for the dual symptomatology of residual upper motor neurone paralysis, but also in some degree for the striking and disconcerting disparities of observation that we find in the *macacus* experimental physiology of this region.

No one conscious of the almost unbelievably complex character of the neuronal connections in the cortex will speculate without diffidence on these problems, but the issue has been raised by the experimental studies referred to, though not solved by them, and therefore an alternative point of view—submitted only tentatively—may be justified.

It should, however, be emphasized that there is as yet no conclusive evidence that isolated interruption of the corticospinal projection system from the motor cortex is not adequate to produce both the negative and the positive symptoms of spastic residual paralysis from cerebral lesion in man, and dogmatic pronouncements to the contrary—based upon the dual hypothesis of Fulton—should be treated with reserve, and it is probable that all the *macacus* experimental work on this subject will

demand repetition and confirmation before we shall be in a position to draw any conclusions from it.

VI.—GENERAL CONCLUSIONS.

"Es vielleicht doch ein Trugschluss ist, in den man gar zu leicht verfallt, wenn man im allgemeinen nach der Grösse der Zellen auch auf ihrer Bedeutung und physiologische Dignität schliessen zu durfen glaubt."—ECONOMO und KOSKINAS, *"Die Cytoarchitektonik der Grosshirnrinde des erwachsenen Menschen,"* 1925.

Perhaps the most important conclusion reached in this review is that the giant cells of Betz do not constitute a specific morphological and physiological category, standing apart from the other large pyramidal cells of cortical areas 4 and 6, or FA and FB. Physiological experiment has failed to show that these cells have exclusive functions not shared by other large pyramidal cells in layer V of these areas. On the contrary, all the evidence is that they do share their functions with these cells. On histological grounds, Economo and Koskinas have come to the conclusion that the giant cells of Betz, the simple giant cells and the large pyramidal cells are of one "Zellart" and differ merely in their size. From their distribution, these observers conclude that the largest giant cells mediate the simple movements of the legs and trunk, and that the finer and more complex movements are subserved by the smallest giant cells and by the large pyramidal cells.

These conclusions make possible a return to realism in our consideration of the structure and functions of the motor cortex, and they clear away the edifice of hypothesis that has been built upon the initial assumption of the specificity of the giant cell of Betz.

It seems, then, that the anatomical basis of the physiologically delimited motor cortex is provided by these three dimensional categories of cell; Betz cell, simple giant cell, large pyramidal cell, as they lie in cortical layer V within the boundaries of the cortical areas named 4 and 6 (or FA and FB). It is from these cells that arise the fibres of the upper motor neurone (corticospinal fibres of the pyramidal tract, and cortical fibres to the motor nuclei of the brain-stem), and the field of distribution of these cells is the field of origin of this category of fibres.

This brings us to the question of the relation of these structures to the familiar cortical areal map.

Reasons have been given for concluding that a correlation of a cortical function with a cortical "area" is not truly a correlation of function with structure. A cortical area is largely a convention, it is certainly not a

structure; indeed it is no more than a two-dimensional representation that seeks to sum the conflicting claims of six independently varying cortical layers. Within a cortical area, one cortical lamina may undergo notable changes, while another lamina may extend unchanged into an adjacent area. Therefore, the correlation of cortical function with cortical structure must be a correlation with cells, fibres, and cell and fibre arrangements in the relevant lamina or laminæ, and in the particular case of the motor cortex it is a correlation with the large pyramidal cells, already defined, that lie in layer V in cortical areas 4 and 6. The attempted correlation of function with "area" is a misapplication of cortical cytoarchitectonics and has proved misleading in this connection.

We have learned, also, that at any rate in man and the anthropoid apes, the motor cortex is one and indivisible and shows no evidence within its borders of the existence of two separate physiological mechanisms, and it merges anteriorly on silent cortex: that is, electrically inexcitable cortex.[1]

The projection tract of this cortex is the pyramidal tract together with the contingent of shorter cortical fibres that pass to the motor nerve nuclei of the brain-stem. The evidence submitted from experiments on *cercopithecus* and *macacus* to the effect that there are two separable motor mechanisms, a "histologically defined motor cortex" and a "premotor" cortex is capable of a simpler interpretation, and is primarily based upon the untenable hypothesis that the Betz cell is a specific entity.

This hypothesis of a dual cortical motor mechanism within the excitable frontal cortex recalls Head's theory of the afferent nervous system in which, also, two separate anatomical sensory mechanisms were postulated, and it seems highly probable that it is a figment of a comparable order.

Turning from this aspect of the subject to the correlation of Betz cells with pyramidal fibres and with the cortical projection fibres to the motor nuclei of the brain-stem, we find a striking discrepancy between the estimated totals of Betz cells with the numerical analyses of the pyramidal fibres, a discrepancy that must be much greater when we take the fibres to the brain-stem also into consideration. Even if we make the most generous allowance for the range of error in Betz cell enumeration inherent in the difficulties that the identification of these cells presents, the discrepancy remains quite remarkable. Further, the pyramidal tract appears

[1] The topographically separate excitable field for primary eye movements is a distinct anatomical mechanism with its own physiological properties.

as predominantly a fine-fibre, and hence a slowly conducting path, and contains a considerable proportion of unmyelinated fibres. In short, it has become impossible to maintain that the Betz cells can provide any more than a proportion of the fibres that make up the pyramidal tract. The method of retrograde degeneration upon which the attribution of pyramidal fibre origin to the Betz cells rests is probably not valid for this purpose since we may not conclude that all the cells the axones of which are divided show reactionary changes.

The question of a consideration of cortical motor function in terms of cortical laminæ has also been raised, and it seems possible that in what we may call a laminar physiology we may find the solution of some of the outstanding obscurities of cortical function. In the present state of knowledge nothing definite can be said on this point.

In conclusion, in a recent review of the anatomy and physiology of cutaneous sensibility, the present writer (1942) referred to the tendency evident in the literature of the subject to postulate anatomical structures in accounting for the phenomena, without attempting to establish whether or not such structures were present, and it appeared in some notable instances that anatomical research had failed to demonstrate their presence. From what has been said in the present review, it is clear that this tendency is not confined to the literature of sensory function, but is much in evidence in current hypotheses of cortical motor function. Here it shows itself by the arbitrary creating of anatomical categories amongst cells and fibres, and the attribution to each of these of exclusive functions. This necessarily involves a multiplication of hypotheses to account for observed phenomena beyond what these require in their generalization. Some of these hypotheses are pure assumptions, others purport to flow from the facts but do not clearly do so. Thus, the current views on cortical motor function have been needlessly complicated and contain a large element of assumption that is not clearly submitted as such.

Accompanying this defect in logical thought, and therefore in scientific method, is the employment of a loose nomenclature; sometimes capable of more than one meaning, as in the current usages of the term "motor cortex"; sometimes having no single clear and unequivocal referent. Of the latter type is the term "giant cell." For approximately seventy years we have taken it for granted that this term referred to a well-defined specific cell category, and we have thus been led to attribute to it specific and exclusive functions. Yet it has never been a term of precision and on examination is found incapable of being made so, since the structure to

which it refers has no specific individuality of the kind postulated for it. When we consider the active and widespread pursuit of neurophysiology, seventy years is an overlong period for an assumption to have remained current without examination, and the reflection arises that perhaps in our haste to add to knowledge, we have sometimes neglected that "unresting contemplation of the facts of observation," and that periodical halting to examine our basic assumptions that are so essential to the building of a stable fabric of ordered knowledge.

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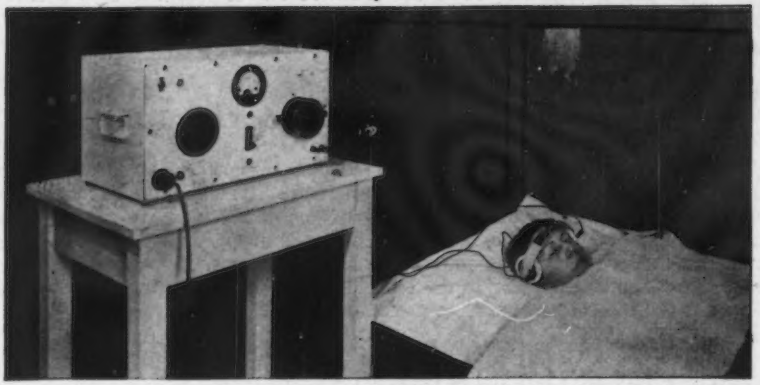

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